112. *Competitive Reactions Involving Formation on Sydnones and Cyclic Anhydrides.*

By F. H. C. STEWART.

The reaction of acetic anhydride with several *N*-nitroso-αα′-iminodiacids and *N*-alkyl-*N*-nitroso-α-amino-acids containing two or three carboxyl groups to form sydnones or cyclic anhydrides has been investigated, and some of the factors influencing the nature of the products are discussed.

CYCLODEHYDRATION, by acetic anhydride, of the *N*-nitroso-derivatives of α′-iminodiacids and *N*-alkyl-*N*-nitroso-α-amino-acids possessing a suitably placed second carboxyl group can lead either to a sydnone or to a cyclic anhydride, and a well-defined example of each of these situations has been reported in the literature. Brookes and Walker [1] found that *N*-benzyl-*N*-nitrosoaspartic acid (I) formed *N*-benzyl-*N*-nitrosoaspartic anhydride rather than the isomeric 3-benzyl-4-carboxymethylsydnone, but Stewart [2] showed that *N*-nitrosoiminodiacetic acid (II; R = H) gave 3-carboxymethylsydnone in high yield. The corresponding cyclic anhydride (III; R = NO) was apparently not formed to an appreciable extent, although the phenyl analogue (III; R = Ph) is readily obtained from *N*-phenyliminodiacetic acid and acetic anhydride.[3] Several analogous competitive situations involving only cyclic anhydrides are also known. Thus, tricarballylic acid with acetic anhydride gives the αβ-anhydride (IV; *n* = 1) rather than the six-membered αα′-isomer, which has not yet been described.[4] Similarly, β-carboxyadipic acid gives the five-membered anhydride (IV; *n* = 2) in preference to the isomeric glutaric anhydride.[5] In order to assess more precisely the tendency of the sydnone system to be produced in competition with

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[1] Brookes and Walker, *J.*, 1957, 4409.

[2] Stewart, *Chem. and Ind.*, 1961, 1411.

[3] Bischoff and Hausdörfer, *Ber.*, 1892, **25**, 2270.

[4] Malachowski, *Bull. Acad. Polon.*, 1929, 265.

[5] Lynn and Roberts, *J. Org. Chem.*, 1961, **26**, 4701.

some cyclic anhydride ring compounds which are structural variations of (I) and (II) have now been studied.

The preferential formation of the sydnone ring from *N*-nitrosoiminodiacetic acid (II; R = H) has been confirmed in the case of the phenyl analogue (II; R = Ph). On treatment with acetic anhydride a mixture of 3-carboxymethyl-4-phenylsydnone (V) and 3-α-carboxybenzylsydnone (VI) was produced in 80% total yield, with the former predominating (50%). There was no evidence of simultaneous formation of a cyclic anhydride (as III). Both these sydnones decomposed vigorously on melting, with evolution of carbon dioxide, and formation of 3-methyl-4-phenylsydnone and 3-benzylsydnone, respectively.

In the *N*-nitrosoiminodiacetic acids (II) either of the carboxyl groups can participate in sydnone formation, whereas with *N*-benzyl-*N*-nitrosoaspartic acid (I) this could only have occurred with the α-carboxyl group. In order to provide a more unambiguous choice between formation of a sydnone or a five-membered anhydride ring, while maintaining the general structural arrangement present in (I), *meso*-αβ-di-(*N*-benzyl-*N*-nitrosoamino)-succinic acid (VII) has been prepared. This compound reacted with acetic anhydride in the cold to give the cyclic anhydride (VIII) instead of a sydnone. When the product (VIII) was boiled with acetic anhydride, however, a second molecule of water was lost with rearrangement to 3,3′-dibenzyl-4,4′-bisydnone (IX). The existence of appreciable electronic interaction between the adjacent sydnone nuclei is indicated by a marked bathochromic displacement of the ultraviolet absorption maximum (350 mμ) from that of an isolated sydnone ring (about 295 mμ).

An attempt to prepare the DL-isomer of the acid (VII) by nitrosation of DL-αβ-di-(*N*-benzylamino)succinic acid resulted in extensive inversion of configuration, and the action of acetic anhydride on the crude nitroso-compound gave the *meso*-anhydride (VIII). Several other instances of the inversion of DL-αβ-diaminosuccinic acid derivatives to the more stable *meso*-isomers under relatively mild acidic conditions have been described.[6,7]

It is known that in sydnone formation an intermediate mixed anhydride between acetic anhydride and the α-carboxyl group is first produced, this reaction being followed by electrophilic attack on the nitroso-group with elimination of acetic acid.[8] The failure of *N*-benzyl-*N*-nitrosoaspartic anhydride, as an internal mixed anhydride, to react further to form a sydnone has been ascribed to steric and polar factors by Brookes and Walker.[1] Similarly, the anhydride (VIII) was stable, except under the vigorous dehydrating conditions mentioned, and its formation from the acid (VII) suggests that a five-membered anhydride ring is preferred to the sydnone system under these mild competitive conditions.

In view of the formation of sydnones rather than cyclic anhydrides (III) from the *N*-nitrosoiminodiacetic acids it was of interest, therefore, to examine the behaviour of an *N*-alkyl-*N*-nitrosoglutamic acid, in which formation of a sydnone would compete with that of a six-membered anhydride ring in a structural environment similar to that present in *N*-benzyl-*N*-nitrosoaspartic acid (I). *N*-Benzylglutamic acid is not described in the literature, but *N*-2′-cyanoethyl-L-glutamic acid, which is readily obtained by cyanoethylation of L-glutamic acid,[9] appeared to be a satisfactory substitute, as the cyanoethyl group has already been incorporated in a sydnone and seemed to confer good crystallising properties.[10] The corresponding nitroso-derivative (X) reacted with acetic anhydride at room temperature, and the glutamic anhydride (XI) was obtained in 46% yield accompanied by the sydnone (XII) in 8% yield. The anhydride (XI) was optically active, and when refluxed with ethyl acetate underwent racemisation with formation of the DL-anhydride rather than the isomeric sydnone (XII). It is noteworthy, however, that the anhydride reacted with an excess of cold water to give the sydnone in 35% yield in addition to the parent

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[6] Wenner, *J. Org. Chem.*, 1948, **13**, 26.

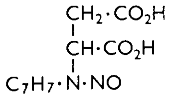
[7] Kuhn and Zumstein, *Ber.*, 1926, **59**, 479.

[8] Baker, Ollis, and Poole, *J.*, 1950, 1542.

[9] McKinney, Uhing, Setzkorn, and Cowan, *J. Amer. Chem. Soc.*, 1950, **72**, 2599.

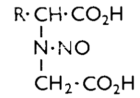
[10] Stewart, *J. Org. Chem.*, 1962, **27**, 687.

nitroso-acid (X). The sydnone was also obtained in low yield (5%) by the action of acetic anhydride on the pure anhydride (XI), which suggests that it is a secondary product in the cyclodehydration of the nitrosoglutamic acid (X), and that a six-membered anhydride ring is formed in preference to the sydnone nucleus under these structural conditions.



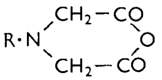
$$\begin{array}{l} CH_2\cdot CO_2H \\ CH\cdot CO_2H \\ C_7H_7\cdot N\cdot NO \end{array}$$

(I)

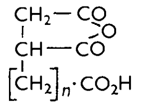


$$\begin{array}{l} R\cdot CH\cdot CO_2H \\ N\cdot NO \\ CH_2\cdot CO_2H \end{array}$$

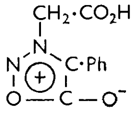
(II)



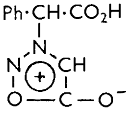
(III)



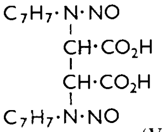
(IV)



(V)

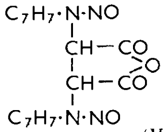


(VI)

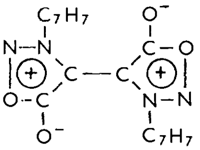


$$\begin{array}{l} C_7H_7\cdot N\cdot NO \\ CH\cdot CO_2H \\ CH\cdot CO_2H \\ C_7H_7\cdot N\cdot NO \end{array}$$

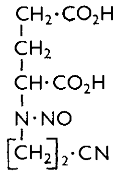
(VII)



(VIII)

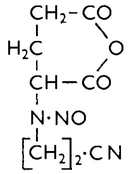


(IX)

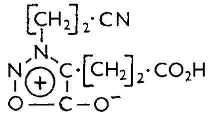


$$\begin{array}{l} CH_2\cdot CO_2H \\ CH_2 \\ CH\cdot CO_2H \\ N\cdot NO \\ [CH_2]_2\cdot CN \end{array}$$

(X)

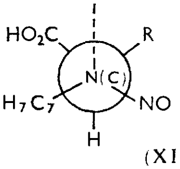


(XI)

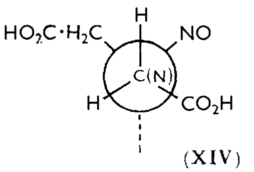


(XII)

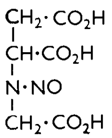
The preferential formation of cyclic anhydrides from compounds (I), (VII), and (X), compared with the exclusive production of sydnones from the *N*-nitrosoiminodiacetic acids (II), may be partly due to conformational factors which tend to favour sydnone formation in the latter series. Consideration of the arrangement of groups about the C_α–N bond in acids (I) and (VII) indicates that the preferred conformation is probably (XIII), in which R represents the remainder of the molecule, and the largest groups are in a *trans*-orientation. In form (XIII), however, the nitroso- and the carboxyl group are not suitably placed for participation in sydnone formation, for which a more strained conformation would have to be adopted. The same argument also applies to the glutamic acid (X). In the case of *N*-nitrosoiminodiacetic acid (II; R = H), on the other hand, the most favourable conformation is (XIV), in which the most bulky groups are again *trans*, but the nitroso-group is here able to participate in sydnone formation without any radical change in the conformation. The situation is rather more complex with *N*-nitroso-α-phenyl-αα′-iminodiacetic acid (II; R = Ph) owing to the increased number of possible conformations and to the non-equivalence of the carboxyl groups, which will result in different reactivities for the derived mixed anhydrides. An additional factor is the possibility of resonance stabilisation in the main reaction product, 3-carboxymethyl-4-phenylsydnone (V), owing to conjugation between the phenyl and the sydnone nuclei. The existence of such conjugation in (V) is confirmed by an appreciable bathochromic displacement of the sydnone absorption maximum (317 mμ) from the corresponding value for (VI) (294 mμ).



(XIII)



(XIV)



$$\begin{array}{l} CH_2\cdot CO_2H \\ CH\cdot CO_2H \\ N\cdot NO \\ CH_2\cdot CO_2H \end{array}$$

(XV)

The above conformational effect is probably not large, but if the other factors concerned are fairly evenly balanced, as appears to be the case when a six-membered anhydride ring is involved, it may be sufficient to influence the course of the reaction. An attempt to incorporate both types of competitive situation in the same molecule, which might have thrown more light on this question, did not give satisfactory results in preliminary experiments. *N*-Carboxymethyl-*N*-nitrosoaspartic acid (XV) reacted with acetic anhydride to form a viscous mixture from which no definite product could be isolated.

The isomerization of the anhydride (XI) in the presence of water is in some respects analogous to the rearrangement of the γ-esters of *N*-acyl-α-glutamyl-peptides in aqueous media to γ-glutamyl-peptides by way of an intermediate cyclic imide,[11] and with this in mind the reactions of compound (XI) and related six-membered cyclic anhydrides are being investigated in detail.

EXPERIMENTAL

N-*Nitroso-α-phenyl-$\alpha\alpha'$-iminodiacetic Acid* (II; R = Ph).—An ice-cold solution of α-phenylimino-$\alpha\alpha'$-diacetic acid hydrochloride [12] (7 g.), prepared by hydrolysis of ethyl (α-cyanobenzylamino)acetate,[13] in water (14 ml.) was treated with a concentrated solution of sodium nitrite (2·1 g.) with stirring. After 30 min. the solution was saturated with sodium chloride and extracted with ethyl acetate. Evaporation of the dried extract gave the *nitroso-compound* (5·77 g., 85%), m. p. 148—149°. Recrystallised from ethyl acetate–hexane, it had the same m. p. (Found: C, 51·0; H, 4·0; N, 11·6. $C_{10}H_{10}N_2O_5$ requires C, 50·4; H, 4·2; N, 11·8%).

3-*Carboxymethyl-4-phenylsydnone* (V).—The foregoing nitroso-compound (5·77 g.) was set aside in acetic anhydride (33 ml.) for 4 days at room temperature, then the mixture was hydrolysed with water (10 ml.), and the whole evaporated to dryness *in vacuo*. The residual oil deposited the *sydnone* (V). This was separated by addition of the minimum quantity of ether necessary to permit filtration, and was washed with ether (yield, 2·27 g., 43%). It formed needles (from water), m. p. 200—201° (decomp.), $\nu_{max.}$ (in KBr) 2700—2500 (CO_2H), 1760 (sydnone CO), 1700 (CO_2H), and 1535 cm.$^{-1}$ (conj. phenyl), $\lambda_{max.}$ (in EtOH) 317 mμ (ε 10,700) (Found: C, 54·6; H, 3·7; N, 13·4. $C_{10}H_8N_2O_4$ requires C, 54·6; H, 3·7; N, 12·7%).

The sydnone (100 mg.) was melted cautiously in a test-tube. When gas evolution had ceased the residue, which contained much tar, was boiled with water and charcoal. The filtered solution deposited 3-methyl-4-phenylsydnone as needles (11 mg., 14%), m. p. 132—134°. Eade and Earl [14] give m. p. 131—132°. The infrared spectrum of the product was identical with that of an authentic sample.

3-α-*Carboxybenzylsydnone* (VI).—The ethereal filtrate from the sydnone (V) was evaporated, and the residue inoculated with 3-α-carboxybenzylsydnone. In the absence of inoculation (as when the preparation was first carried out) crystallisation was slow. The *sydnone* was separated from oil by treatment with ether as before, and was washed with ether (1·25 g., 23%). It formed prisms [from water in which it was more soluble than the isomer (V)], m. p. 137—138° (decomp.), $\nu_{max.}$ (in KBr) 3180 (sydnone CH), 2700—2430 (CO_2H), 1760 (sydnone CO), and 1675 cm.$^{-1}$ (CO_2H), $\lambda_{max.}$ (in EtOH) 294 mμ (ε 7000). Recrystallised from ethyl acetate–hexane, it had m. p. 140—141° (decomp.) (Found: C, 54·5; H, 3·6; N, 13·3. $C_{10}H_8N_2O_4$ requires C, 54·6; H, 3·7; N, 12·7%).

Further treatment of the ethereal residue after separation of this compound yielded a mixture of sydnones (V) and (VI) (0·72 g., 14%), which by infrared analysis was found to contain about 50% of each. An unidentified acidic oil (0·7 g.) remained, which did not give the Liebermann reaction.

Pyrolysis of 3-α-carboxybenzylsydnone (100 mg.) as before, followed by distillation *in vacuo*, gave 3-benzylsydnone, which, recrystallised from ethyl acetate–hexane, had m. p. 67—68° (35 mg., 44%), $\nu_{max.}$ (in Nujol) 3150 (sydnone CH) and 1740 cm.$^{-1}$ (sydnone CO). Baker, Ollis, and Poole [15] give m. p. 69·5°.

meso-$\alpha\beta$-*Di*-(N-*benzyl*-N-*nitrosoamino*)*succinic Anhydride* (VIII).—A solution of *meso*-$\alpha\beta$-di-(*N*-benzylamino)succinic acid [6] (1·0 g.) in concentrated hydrochloric acid (4·0 ml.) and water (6·0 ml.) was cooled in ice–salt and nitrosated with a concentrated solution of sodium nitrite

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[11] Battersby and Robinson, *J.*, 1955, 259.
[12] Stadnikoff, *Ber.*, 1908, **41**, 4364.
[13] Scheibler and Baumgarten, *Ber.*, 1922, **55**, 1358.
[14] Eade and Earl, *J.*, 1948, 2307.
[15] Baker, Ollis, and Poole, *J.*, 1949, 307.

(0·46 g.). The dinitroso-derivative (VII) separated as a viscous mass which was extracted with ethyl acetate, with addition of urea to remove the excess of nitrous acid. Evaporation of the dried extract gave a yellow *dinitrosoamino-acid* (0·91 g., 77%) that, crystallised (with difficulty) from ethyl acetate–hexane, had m. p. 123—124° (decomp.) (Found: C, 55·8; H, 5·0; N, 13·9. $C_{18}H_{18}N_4O_6$ requires C, 56·0; H, 4·7; N, 14·5%).

Treatment of the nitroso-derivative (370 mg.) with acetic anhydride (1·3 ml.) for 2—3 days at room temperature gave a crystalline precipitate of the *anhydride* (VIII) (173 mg., 49%), which recrystallised from ethyl acetate–hexane as needles, m. p. 126—127° (decomp.), $\nu_{max.}$ (in KBr) 1880 and 1800 cm.$^{-1}$ (CO·O·CO), $\lambda_{max.}$ (in $CHCl_3$) 250 mμ (ε 13,600). It gave a strong Liebermann reaction (Found: C, 58·9; H, 4·2; N, 14·9. $C_{18}H_{16}N_4O_5$ requires C, 58·7; H, 4·3; N, 15·2%). A further 15 mg. (4%) of less pure material, accompanied by an oil which did not give the Liebermann reaction, was obtained by evaporation of the mother-liquor.

Similar treatment of DL-αβ-di-(*N*-benzylamino)succinic acid [6] yielded a non-crystalline nitroso-derivative, which with acetic anhydride formed the above *meso*-anhydride in 38% overall yield. The infrared spectra of the two products were identical.

3,3′-*Dibenzyl*-4,4′-*bisydnone* (IX).—The anhydride (VIII) (450 mg.) was heated with acetic anhydride (3·0 ml.). Slight effervescence occurred near the b. p. and the solution was then refluxed for 1—2 min. Most of the acetic anhydride was removed *in vacuo*, and the mixture hydrolysed with boiling water and filtered hot. The *sydnone* (IX) remained on the filter and was washed with hot ethanol (177 mg., 41%). It formed needles (from ethyl acetate–hexane), m. p. 172·5—173·5°, $\nu_{max.}$ (in KBr) 1750 cm.$^{-1}$ (sydnone CO), $\lambda_{max.}$ (in $CHCl_3$) 350 mμ (ε 14,700) (Found: C, 61·8; H, 4·0; N, 15·9. $C_{18}H_{14}N_4O_4$ requires C, 61·7; H, 4·0; N, 16·0%). The infrared spectrum had many features in common with that of 3-benzylsydnone.

Reaction of N-2′-*Cyanoethyl*-N-*nitroso*-L-*glutamic Acid* (X) *with Acetic Anhydride*.—An ice-cold solution of freshly prepared *N*-2′-cyanoethyl-L-glutamic acid monohydrate [9] (5·0 g.) and concentrated hydrochloric acid (2·0 ml.) in water (6·0 ml.) was nitrosated with a concentrated aqueous solution of sodium nitrite (1·7 g.), saturated with sodium chloride after 30 min., and extracted with ethyl acetate, with addition of urea. Evaporation of the dried extract gave the nitroso-compound (X) as an almost colourless oil, $\nu_{max.}$ (film) 2750—2550 (CO_2H), 2270 (CN), 1730 (CO_2H), 1460, and 1045 cm.$^{-1}$ (NO). The product gave a strong Liebermann reaction.

The crude nitroso-compound was dissolved in acetic anhydride (18 ml.) at room temperature. N-2′-*Cyanoethyl*-N-*nitroso*-L-*glutamic anhydride* (XI) separated as needles. After 24 hr. the mixture was diluted with ether until a faint permanent turbidity developed, and the precipitated anhydride collected (2·2 g., 46%; m. p. 108—109°). Recrystallised from acetic anhydride—ether, it had m. p. 108—109°, $\nu_{max.}$ (in KBr) 2250 (CN), 1830, 1770 (CO·O·CO), and 1405 cm.$^{-1}$ (NO), $[\alpha]_D^{24}$ −72° (*c* 1·0 in ethyl acetate) (Found: C, 45·5; H, 4·2; N, 20·3. $C_8H_9N_3O_4$ requires C, 45·5; H, 4·3; N, 19·9%). The anhydride gave the Liebermann reaction. It tended to absorb moisture slowly from the atmosphere but could be kept unchanged indefinitely in a desiccator.

The filtrate from the anhydride was evaporated and diluted to 20 ml. with acetic anhydride. An aliquot part (2 ml.) was hydrolysed with water, and the mixture evaporated to dryness *in vacuo*. The residue partially solidified and was washed with ethyl acetate and ether, to give 4-2′-*carboxyethyl*-3-2′-*cyanoethylsydnone* (XII) as needles (40 mg., 8%) which, recrystallised from ethanol–ether, had m. p. 128·5—129·5°, $\nu_{max.}$ (in KBr) 3000, 2700—2500 (CO_2H), 2250 (CN), 1750 (sydnone CO), and 1700 cm.$^{-1}$ (CO_2H), $\lambda_{max.}$ (in EtOH) 296 mμ (ε 9500) (Found: C, 45·6; H, 4·2; N, 19·8. $C_8H_9N_3O_4$ requires C, 45·5; H, 4·3; N, 19·9%). The sydnone did not give the Liebermann reaction.

After 48 hr. a further 2 ml. portion gave 8 mg. (1·6%) of the sydnone; after 3 days the remainder of the mixture was worked up, but no further sydnone could be isolated.

When the sydnone was refluxed with ethyl acetate for 4 hr. much decomposition occurred and only 50% of the starting material was recovered.

Experiments with N-2′-*Cyanoethyl*-N-*nitroso*-L-*glutamic Anhydride* (XI).—(*a*) The anhydride (200 mg.) was refluxed with ethyl acetate (20 ml.) for 4 hr., by which time the optical activity of the solution had disappeared and a violet tint had developed. Evaporation *in vacuo* gave the DL-anhydride as a colourless solid (161 mg., 81%), m. p. 112—113° (from acetic anhydride–ether). This absorbed moisture from the atmosphere and did not give a satisfactory analysis (Found: C, 43·5; H, 4·6%). The infrared spectrum was almost identical with that of the L-isomer (XI), apart from some minor intensity differences in the 1400—900 cm.$^{-1}$ region.

(*b*) A solution of the anhydride (200 mg.) in acetic anhydride (2 ml.) was kept for 24 hr. at room temperature, then worked up in the usual way; unchanged anhydride (119 mg., 60%) and the sydnone (XII) (10 mg., 5%) were obtained accompanied by oily by-products.

(*c*) The anhydride (500 mg.) was treated with water (1—2 ml.) for several hours at room temperature. The solid dissolved slowly, and the water was then removed *in vacuo*. The residue was treated with ethyl acetate, and the sydnone collected (172 mg., 35%). Evaporation of the filtrate gave the nitroso-acid (X) as a yellow oil. The infrared spectrum was almost identical with that of the product obtained by direct nitrosation of *N*-2′-cyanoethyl-L-glutamic acid.

N-*Carboxymethyl*-N-*nitrosoaspartic Acid* (XV).—A solution of *N*-carboxymethylaspartic acid [16] (1·7 g.) in water (8·5 ml.) was saturated with nitrous fumes at room temperature. When a drop of the mixture no longer became turbid on dilution with acetone it was evaporated *in vacuo*. The residue was dissolved in ethyl acetate, dried (Na_2SO_4), and recovered. The *nitroso-compound* remained; when washed with hexane, it (1·8 g., 93%) had m. p. 153—154° (decomp.), unchanged by recrystallisation from ethyl acetate–hexane (Found: C, 32·9; H, 3·5; N, 13·3. $C_6H_8N_2O_7$ requires C, 32·7; H, 3·7; N, 12·7%).

The nitroso-derivative (XV) was set aside in acetic anhydride (15 ml.) for 4—5 days. A dark red solution was obtained, which was hydrolysed with water (5 ml.) and evaporated *in vacuo*. The residue was dissolved in ethyl acetate, then dried (Na_2SO_4) and recovered *in vacuo*. Addition of a little ether precipitated a buff, highly hygroscopic, solid (0·18 g.), and removal of the ether left a very viscous syrup whose infrared spectrum contained broad carbonyl absorption around 1740 cm.$^{-1}$. This product was acidic and gave a very weak Liebermann reaction. It formed an insoluble copper salt in which the carbonyl absorption was displaced largely to 1600 cm.$^{-1}$, characteristic of ionised carboxyl. Weak residual absorption remained at 1745 cm.$^{-1}$, which suggests that a little sydnone may be present in the mixture.

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[16] Laliberté and Berlinguet, *Canad. J. Chem.*, 1962, **40**, 163.