Nitrogen-containing Carbohydrate Derivatives. Part XXXII.[1] Further Studies on the Ring-opening of Epimino-sugars

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Study of the ring-opening reactions of derivatives of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allosides with azide ion has shown that these are normal (*i.e.* major diaxal opening) and not 'abnormal' (*i.e.*, major diequatorial opening) as previously reported. Some ring-opening reactions of the corresponding mannosides are also reported.

In previous papers of this series the ring-opening reactions of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-mannopyranoside (1a), its *allo*-analogue (4a), and various *N*-substituted derivatives have been reported. In this paper comment is made on particular aspects of our previous experimental results, some of which have now been shown to be erroneous.

RESULTS AND DISCUSSION

We have reported [2] that treatment of the *N*-benzoylepiminomannoside (1b) with sodium azide and ammonium chloride in boiling *NN*-dimethylformamide (DMF) gave a mixture of methyl 3-azido-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altropyranoside (2b) (20%) and methyl 4,6-*O*-benzylidene-2,3-dideoxy-2'-phenyl-α-D-mannopyranosido[2,3-*d*]-$\Delta^{3'}$-oxazoline (3b) (36%). Repetition of this experiment many times under the above conditions has given only *one* component, methyl 3-azido-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altroside (2b) (80%); no oxazoline (3b) was detected. However, with no ammonium chloride present, that is, under more basic conditions, we obtained a result similar to that previously reported: the major product was the oxazoline (3b) (48%), obtained along with the ring-opened *altro*-derivative (2b) (15%). Thus the discrepancies between the published [2] and the present work can be explained by assuming that in the former the ammonium chloride was not in fact included in the reaction mixture.

In attempts to explore such ring openings further the reactions were extended to the *N*-*p*-anisoyl (1c) and *N*-*p*-nitrobenzoyl (1d) derivatives of the 2,3-epimino-mannoside (1a). When treated with sodium azide and ammonium chloride in DMF, the *N*-*p*-anisoyl derivative (1c) gave only methyl 3-azido-2,3-dideoxy-2-*p*-methoxybenzamido-α-D-altropyranoside (2c). With no ammonium chloride present, the oxazoline (3c) was the major product, with the 3-azidoaltroside (2c) being formed in low yield.

Extensive decomposition of the *p*-nitrobenzoyl derivative (1d) was observed under the two sets of conditions previously used. Only methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-*p*-nitrobenzamido-α-D-altropyranoside (2d) was isolated from either reaction, in 45% yield in the presence and 25% in the absence of ammonium chloride.

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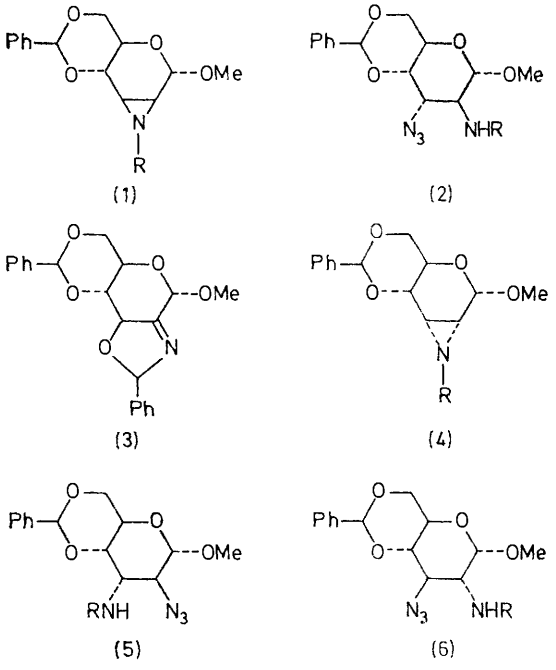
We reported previously [2] that azidolysis (ammonium chloride present) of the *N*-benzoylepiminoalloside (4b) gave methyl-3-azido-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside (6b) (70% yield) by an



a; R = H
b; R = Bz
c; R = C_6H_4·OMe-*p*
d; R = C_6H_4·NO_2-*p*

'anomalous' diequatorial ring opening; no diaxially-opened product was observed. Repetition of this reaction many times has yielded two products. Recrystallisation of the crude product from propan-2-ol gave white needles of methyl 3-azido-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside (6b) (18%); the mother liquors yielded methyl 2-azido-3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altropyranoside (5b) (56%) [identical with that obtained from benzoylation of (5a)]. N.m.r. analysis of the crude product mixture showed the ratio of (5b) to (6b) to be 74 : 26. The altropyranoside (5b) was unchanged when

[1] Part XXXI, C. L. Brewer and R. D. Guthrie, *J.C.S. Perkin I*, 1974, 657.
[2] R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 1965, 3828.

heated in DMF for 3 h; thus there was no isomerisation of *altro*- to *gluco*-products under the conditions of the reactions. Hence we now find that this opening is, in fact, ' normal ', the major product being the diaxially ring-opened product, even though it is accompanied by a significant amount of the product from diequatorial opening.

Our inference [2] that ' anomalous ' opening was taking place can be explained by the fact that the yield quoted (70%) was the yield of crude material, and the possibly erroneous assumption was made that the product from crystallisation was typical of the whole product [t.l.c. and n.m.r. techniques were not available when the original experiment was carried out (1962)]. We apologise for this poor experimentation. The reaction performed with no ammonium chloride present gave the same ratio of products (n.m.r. analysis).

With sodium azide and ammonium chloride in DMF the *N*-*p*-anisoylepiminoalloside (4c) gave the *altro*- (5c) and *gluco*- (6c) products in the ratio 71 : 29 (n.m.r. analysis) which was changed only slightly (to 65 : 35) when the reaction was repeated without ammonium chloride present. Thus again the major product was that formed by diaxial opening.

As in the *manno*-series, the *p*-nitrobenzoylepiminoalloside (4d) was difficult to handle and had a tendency to decompose. However, azidolysis in the presence of ammonium chloride gave two major products with many minor components; these were separated by p.l.c. The major product was shown to be methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-*p*-nitrobenzamido-α-D-altropyranoside (5d), formed together with methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-*p*-nitrobenzamido-α-D-glucopyranoside (6d) in the ratio 78 : 14. When this reaction was repeated without ammonium chloride, t.l.c. showed the presence of at least four major products and many minor ones. Thus, any analyses of these mixtures obtained for the diaxially and diequatorially opened products as above would not have had much meaning.

No oxazoline was detected in any of these reactions in the *allo*-series. The *N*-benzoylepiminoalloside (4b) was unchanged when heated in DMF; no evidence for thermal isomerisation was detected (*cf.* ref. 3).

The ring opening of the epiminomannosides (1b—d) with sodium azide in the presence of ammonium chloride, resulting in products of *trans*-diaxial ring opening only, is consistent with the results of other workers; [4,5] Ponsold *et al.*[6] treated 2,3-benzoylepiminocholestane with sodium azide and ammonium chloride in DMF and found *trans*-diaxial opening only, with no isomerisation to an oxazoline.

The pattern of ring opening in the 2,3-epiminoallosides (4) and their anomers has proved unpredictable. Explanation of all the results known is difficult. Extension of the ring opening reactions of (4a) to the derivatives (4b—d) with sodium azide is important in that it shows that the ' normal ' pattern of opening is followed, that is, that diaxial opening is preferred, with the ' anomalous ' product present as a significant, but minor, component.

The absence of ammonium chloride, *i.e.* mildly basic conditions, again had little noticeable effect on the products.

Since the ring opening of the *N*-benzoylepiminoalloside (4b) [2] has now been shown to be ' normal ', it is possible to make the generalisation that most ring-opening reactions of the 2,3-epiminopyranosides with sodium azide, *etc.*, occur in predominantly *trans*-diaxial fashion, although the product of diequatorial opening may also be present. Exceptions to this general rule are the results of Meyer zu Reckendorf,[7] who showed that the base-catalysed ring opening of methyl 2,3-benzoylepimino-4,6-*O*-benzylidene-2,3-dideoxy-β-D-allopyranoside [β-analogue of (4b)] with sodium azide (and with potassium acetate, potassium thioacetate, or alumina) gave products of the D-*gluco*-configuration. Hough and Richardson *et al.*[5] found that ' anomalous ' diequatorial ring-opening occurred when the free *allo*-epimine (4a) was treated with the ammonium halides (except the fluoride) in DMF. However, with the *N*-substituted derivatives, diaxial ring opening predominated, although diequatorial ring opening was significant. Ring-opening reactions of the *N*-acetyl and *N*-mesyl derivatives of (4a) occurred *trans*-diequatorially and *trans*-diaxially, respectively. However many of the published product yields in these ' anomalous reactions ' are very low (often as little as 40% total recovery); thus, generalisation may be dangerous.

EXPERIMENTAL

Solvents were evaporated off under reduced pressure at bath temperatures <50 °C. T.l.c. and p.l.c. were carried out on Merck silica gel GF_{254}. Optical rotations were measured with a Perkin-Elmer 141 instrument for solutions in chloroform at 22 °C. N.m.r. spectra were determined with Varian HA100, A60, and T-60 spectrometers.

Azidolysis of Methyl 2,3-*Benzoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannopyranoside* (1b).—(i) *In the presence of ammonium chloride.* The *N*-benzoylepiminomannoside (1b) (200 mg), sodium azide (150 mg), and ammonium chloride (50 mg) were heated under reflux for 3 h in dry DMF. The solution was then evaporated, and the remaining solid extracted with hot ethyl acetate (3 × 100 ml). The extracts were dried and evaporated to give a solid (83%). T.l.c. showed this to contain one product. Recrystallisation from propan-2-ol gave methyl 3-azido-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altropyranoside (2b), m.p. and mixed m.p. 191—192°, $[\alpha]_D$ −42° (*c* 2) {lit.,[2] m.p. 191—193°, $[\alpha]_D$ −44.7° (*c* 0.81)}.

(ii) *In the absence of ammonium chloride.* T.l.c. showed the product to consist of two components which were separated by p.l.c. (chloroform–light petroleum, 1 : 1). The

[3] Z. M. El Shafei and R. D. Guthrie, *J. Chem. Soc.* (*C*), 1970, 843.

[4] D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 1965, 2736; B. R. Baker and T. L. Hullar, *J. Org. Chem.*, 1965, **30**, 4049; C. F. Gibbs and L. Hough, *Carbohydrate Res.*, 1971, **18**, 363.

[5] Y. Ali, A. C. Richardson, C. F. Gibbs, and L. Hough, *Carbohydrate Res.*, 1968, **7**, 255.

[6] G. Drefahl, K. Ponsold, and D. Klemm, *J. prakt. Chem.*, 1968, **88**, 168.

[7] W. Meyer zu Reckendorf, *Chem. Ber.*, 1964, **97**, 325.

band of higher R_F value gave methyl 4,6-*O*-benzylidene-2,3-dideoxy-2′-phenyl-α-D-mannopyranosido[2,3-*d*]-$\Delta^{2'}$-oxazoline (3b) (48%). Recrystallisation from ethanol gave a white solid, m.p. 151—152°, $[\alpha]_D$ −69° (*c* 2.095) {lit.,[2] m.p. 148—149°, $[\alpha]_D$ −65.6° (*c* 1.13)}. The band of lower R_F value gave the altropyranoside (2b) (15%); m.p. 187—189° (from propan-2-ol), $[\alpha]_D$ −42° (*c* 2.02).

Azidolysis of Methyl 2,3-p-*Anisoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannopyranoside* (1c).—(i) *In the presence of ammonium chloride.* The *N*-*p*-anisoylepiminomannoside (1c) (500 mg), sodium azide (400 mg), and ammonium chloride (175 mg) were refluxed in dry DMF for 3 h. Pouring into ice–water gave a white solid which was filtered off and dried. T.l.c. showed this to consist of one component only, namely *methyl* 3-*azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*methoxybenzamido*-α-D-*altroside* (2c) (70%), which was recrystallised from methanol–water; m.p. 125—126°, $[\alpha]_D$ −70° (*c* 2.04), τ ($CDCl_3$) 2.1—3.15 (9 H, m, aromatic), 3.55br (1 H, d, NH), 4.44 (1 H, s, PhC*H*), 5.3—6.1 (10 H, m, ring protons and *p*-MeO), and 6.57 (3 H, s, 1-OMe) (Found: C, 60.1; H, 5.5; N, 12.8. $C_{22}H_{24}N_4O_6$ requires C, 60.0; H, 5.45; N, 12.7%).

(ii) *In the absence of ammonium chloride.* T.l.c. showed the product mixture to contain two components, which were separated by p.l.c. (benzene–ethyl acetate, 9 : 1). The band of higher R_F value gave the oxazoline (3c) (47%), m.p. 180—182° (from methanol–water), $[\alpha]_D$ −90° (*c* 0.465) {lit.,[3] m.p. 183—184°, $[\alpha]_D$ −83.2 (*c* 0.95)}. The band of lower R_F value gave the altropyranoside (2c) (11 mg), m.p. 124—125°.

Azidolysis of Methyl 4,6-O-*Benzylidene*-2,3-*dideoxy*-2,3-p-*nitrobenzoylepimino*-α-D-*mannopyranoside* (1d).—(i) *In the presence of ammonium chloride.* The *p*-nitrobenzoylepiminomannoside (1d) (350 mg), sodium azide (300 mg), and ammonium chloride (125 mg) were refluxed for 3 h in dry DMF (15 ml). Pouring into ice–water gave a gel which was extracted with chloroform (3 × 100 ml). The extracts were washed with water, dried, and evaporated to give a yellow solid (250 mg). T.l.c. showed it to contain one major product, together with at least six minor components. The major product was purified by p.l.c. (benzene–ethyl acetate, 9 : 1) to give *methyl* 3-*azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*nitrobenzamido*-α-D-*altropyranoside* (2d) (45%), m.p. 229—230° (from propan-2-ol), $[\alpha]_D$ −65° (*c* 0.66); τ (C_5D_5N) 4.56 (1 H, s, PhC*H*), 5.18 (1 H, s, $J_{1,2}$ *ca.* 1 Hz, H-1), and 6.76 (3 H, s, OMe) (Found: C, 55.4; H, 4.9; N, 15.2. $C_{21}H_{21}N_5O_7$ requires C, 55.4; H, 4.65; N, 15.5%). Two other bands were extracted; the products, obtained in low yields, were not characterised.

(ii) *In the absence of ammonium chloride.* The crude product (280 mg), which t.l.c. showed to contain two major products with a large number of minor products, was purified by p.l.c. The major band gave the altropyranoside (2d) (90 mg), m.p. 226—227°, $[\alpha]_D$ −70° (*c* 1).

Methyl 2-*Azido*-3-*benzamido*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*altropyranoside* (5b).—Methyl 3-amino-2-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altroside [2] (400 mg) was dissolved in dry pyridine (10 ml) and benzoic anhydride (500 mg) was added. The solution was stirred at room temperature for 1 h. Work-up gave a syrup (420 mg); this was purified by p.l.c. (chloroform) to give the syrupy *altropyranoside* (5b) (78%), $[\alpha]_D$ +43° (*c* 0.99); τ ($CDCl_3$) 2.05—2.94 (10 H, m, aromatic), 4.34 (1 H, s, PhC*H*), 5.16br (1 H, d, NH), 5.26 (1 H, s, H-1), 5.4—6.4 (6 H, m, ring protons), and 6.53 (3 H, s, 1-OMe) (Found: C, 61.65; H, 5.6; N, 13.2. $C_{21}H_{22}N_4O_5$ requires C, 61.5; H, 5.4; N, 13.7%).

Methyl 2-*Azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-3-p-*nitrobenzamido*-α-D-*altropyranoside* (5d).—Methyl 3-amino-2-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-altropyranoside [2] (200 mg) was dissolved in dry pyridine, *p*-nitrobenzoyl chloride was added and the whole was stirred at room temperature for 1 h. Work-up gave a crystalline compound which was recrystallised from chloroform–petroleum to yield the *altropyranoside* (5d) (75%), m.p. 105—107°, $[\alpha]_D$ +53° (*c* 1.96), τ ($CDCl_3$) 1.6—2.7 (9 H, m, aromatic), 4.33 (1 H, s, PhC*H*), 4.9—5.3 (2 H, m, $J_{1,2}$ 1 Hz, H-1 and NH), 5.5—6.25 (6 H, m, ring protons), and 6.48 (3 H, s, 1-OMe) (Found: C, 55.7; H, 4.7; N, 15.3. $C_{21}H_{21}N_5O_7$ requires C, 55.4; H, 4.65; N, 15.4%).

Azidolysis of Methyl 2,3-*Benzoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*allopyranoside* (4b).—(i) *In the presence of ammonium chloride.* The *N*-benzoylepiminoalloside (4b) (500 mg), ammonium chloride (125 mg), and sodium azide (400 mg) were boiled under reflux in dry DMF (10 ml) for 3 h. The mixture was thrown into ice–water to give a white solid, which was filtered off, washed with water, dried, and recrystallised from propan-2-ol to give methyl 3-azido-2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside (6b) (18%), m.p. 233—235°, $[\alpha]_D$ +76° (*c* 0.61) {lit.,[2] m.p. 233—235°, $[\alpha]_D$ +79.4° (*c* 0.63)}; τ ($CDCl_3$) 2—2.7 (10 H, m, aromatic), 3.3—3.7br (1 H, d, NH), 4.38 (1 H, s, PhC*H*), 5.22 (1 H, d, $J_{1,2}$ 3.5 Hz, H-1), 5.4—5.75 (2 H, m, ring protons), 5.8—6.45 (4 H, m, ring protons), and 6.58 (3 H, s, 1-OMe) (Found: C, 61.6; H, 5.5; N, 13.5. $C_{21}H_{22}N_4O_5$ requires C, 61.5; H, 5.4; N, 13.7%).

The mother liquor was evaporated to a syrup shown to be the altropyranoside (5b) (56%), $[\alpha]_D$ +46° (*c* 1.51), by comparison with the material described above.

(ii) *In the absence of ammonium chloride.* T.l.c. showed the crude product (490 mg) to contain two components in the proportions 74 : 26 (n.m.r.). Recrystallisation from propan-2-ol gave the glucopyranoside (6b), m.p. 231—233°; the mother liquors yielded the syrupy altropyranoside (5b).

Azidolysis of Methyl 2,3-*p*-*Anisoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*allopyranoside* (4c).—(i) *In the presence of ammonium chloride.* The *N*-*p*-anisoylepiminoalloside (4c) (540 mg), sodium azide (400 mg), and ammonium chloride (125 mg) were refluxed for 3 h in dry DMF (10 ml). Pouring into ice–water gave a white solid which was filtered off, washed with water, and dried (450 mg). T.l.c. showed this to consist of two components in the ratio 71 : 29 (n.m.r. analysis). They were separated and purified by p.l.c. (chloroform–light petroleum, 2 : 1). The band of higher R_F value gave syrupy *methyl* 2-*azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-3-p-*methoxybenzamido*-α-D-*altropyranoside* (5c), τ ($CDCl_3$) 2.5—3.3 (9 H, m, aromatic), 4.37 (1 H, s, PhC*H*), 5.11br (1 H, d, NH, *J* 9 Hz), 5.32br (1 H, s, H-1), 5.6—6.35 (9 H, m, ring protons, *p*-OMe), and 6.54 (3 H, s, 1-OMe) (Found: C, 59.6; H, 5.5; N, 12.6. $C_{22}H_{24}N_4O_6$ requires C, 60.0; H, 5.5; N, 12.7%). The lower R_F band gave *methyl* 3-*azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*methoxybenzamido*-α-D-*glucopyranoside* (6c), m.p. 230—245° (decomp.); τ ($CDCl_3$) 2.03—3.2 (9 H, m, aromatic), 3.7br (1 H, d, NH, *J* 9 Hz), 4.38 (1 H, s, PhC*H*), 5.23 (1 H, s, $J_{1,2}$ 3.5 Hz, H-1), 5.3—6.3 (9 H, m, ring protons and *p*-OMe), and 6.58 (3 H, s, 1-OMe) (Found: N, 13.1. $C_{22}H_{24}N_4O_6$ requires N, 12.7%).

(ii) *In the absence of ammonium chloride.* T.l.c. showed the crude product (120 mg) to consist of two components in

the ratio 65 : 35 (n.m.r. analysis). P.l.c. gave the altropyranoside (5c) and the glucopyranoside (6c), m.p. 235—245° (decomp.).

Azidolysis of Methyl 4,6-O-*Benzylidene*-2,3-*dideoxy*-2,3-p-*nitrobenzoylepimino*-α-D-*allopyranoside* (4d).—(i) *In the presence of ammonium chloride.* The *N*-*p*-nitrobenzoylepiminoalloside (4d) (500 mg), sodium azide (400 mg), and ammonium chloride (125 mg) were refluxed in dry DMF for 3 h. Extensive decomposition was observed and the solution colour went from yellow to dark brown. The mixture was evaporated and the residue extracted with hot ethyl acetate. The extracts were filtered and evaporated to give a brown solid (490 mg); t.l.c. showed the presence of two major and many minor components, which were separated by p.l.c. (chloroform–light petroleum, 1 : 1). Extraction of the major band of higher R_F value gave methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-*p*-nitrobenzamido-α-D-altropyranoside (5d) (85%), m.p. 105—106°, $[\alpha]_D$ +54° (*c* 2.12), identical with the authentic compound described above.

The major band of lower R_F value yielded *methyl* 3-*azido*-4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*nitrobenzamido*-α-D-*glucopyranoside* (6d) (15%), m.p. 258—259°, $[\alpha]_D$ +74° (*c* 1.54); τ ($CDCl_3$) 1.6—2.9 (9 H, m, aromatic), 3.3—3.8br (1 H, s, NH), 4.32 (1 H, s, PhC*H*), 5.21 (1 H, s, $J_{1,2}$ 3.8 Hz, H-1), 5.4—6.4 (6 H, m, ring protons), and 6.51 (3 H, s, 1-OMe) (Found: C, 55.4; H, 4.5; N, 15.6. $C_{21}H_{21}N_5O_7$ requires C, 55.4; H, 4.65; N, 15.4%).

(ii) *In the absence of ammonium chloride.* T.l.c. showed the dark brown solid (480 mg) to contain four major and at least twelve minor components.

Action of Heat on Methyl 2,3-*Benzoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*allopyranoside* (4b).—The *N*-benzoylepiminomannoside (4b) (100 mg) was heated alone in dry DMF for 3 h. T.l.c. then showed starting material only. The mixture was evaporated to give white needle-like crystals of starting material (95%), m.p. 190—192°.

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