The Use of Polyphosphoric Ester and Polyphosphoric Acid in the Synthesis of 1,4-Dihydro-4-oxoquinolines

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The synthesis of 1-alkyl-1,4-dihydro-4-oxoquinolines by the cyclization of derivatives of 2-(*N*-alkylanilino)acrylic acid in the presence of polyphosphoric acid or ester has been investigated. The results indicate that polyphosphoric ester is a more efficient reagent for the cyclization of 2-(*N*-alkylanilino)acrylic acid derivatives than polyphosphoric acid and also has advantages over the thermal cyclization.

OUR interest in pharmacologically active alkaloids with the 1-alkyl-1,4-dihydro-4-oxoquinoline skeleton, *e.g.* echinopsine [1] and acronycine,[2] has led us to synthesize analogous compounds. The formation of the 4-hydroxyquinoline system by thermal cyclization [3,4] of 2-anilinoacrylates is limited [5,6] to cases where the aniline nitrogen atom is unsubstituted and there is at least one ethoxycarbonyl group that can participate in the cyclization. To prepare 1-alkyl-1,4-dihydro-4-oxoquinolines by this method, the ring nitrogen atom must be alkylated after cyclization. In the case of polyfunctional 4-hydroxyquinolines a selective alkylation would be exceedingly difficult to achieve. Consequently we have investigated the cyclization of 1-substituted 2-(*N*-alkylanilino)acrylic acid derivatives as a relatively simple means of providing 1-alkyl-1,4-dihydro-4-oxoquinolines. Oxolinic acid (6), an antibacterial agent,[7] was selected as the synthetic objective to test the utility of the method.

The starting material (2) was prepared in good yield

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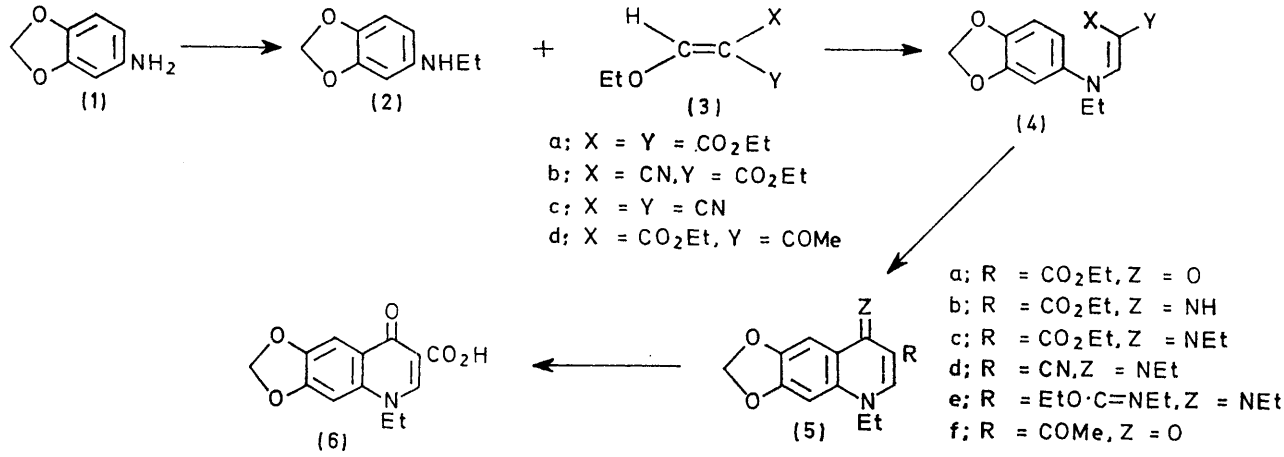
by reductive alkylation of 3,4-methylenedioxyaniline (1) with acetaldehyde, using Raney nickel as the catalyst. *N*-Ethyl-3,4-methylenedioxyaniline (2) on treatment with ethyl 2-ethoxy-1-ethoxycarbonylacrylate (3a) and the similar compounds (3b—d) either with or without a catalyst gave the 1-substituted 2-(*N*-ethyl-3,4-methylenedioxyanilino)acrylic acid derivatives (4a—d) in high yield. For example the ester (3d) on condensation with



(2) in refluxing tetrahydrofuran afforded ethyl 1-acetyl-2-(*N*-ethyl-3,4-methylenedioxyanilino)acrylate (4d) in 88% yield.

T.l.c. and n.m.r. spectral evidence strongly suggested that the products were homogeneous. Geometrical isomerism in these substituted acrylic acid derivatives is not to be expected because (owing to the low energy barrier [8] to rotation about the carbon–carbon double bond) isomerization occurs readily [8] under the conditions of the cyclization.

The esters (3a) and (3b) did not condense with (2) in refluxing dioxan; however the reactions proceeded readily in the presence of a catalytic amount of Triton B (methanolic 40% solution) to afford compounds (4a) and (4b), respectively. The dinitrile (3c) under the same conditions, gave mainly intractable polymers and 1-cyano-2-(*N*-ethyl-3,4-methylenedioxyanilino)acrylonitrile (4c) was obtained in 10% yield only. Eventually, anhydrous zinc chloride was found to be an effective catalyst of the reaction. In the presence of 2 mol. equiv. of anhydrous zinc chloride in tetrahydrofuran the product was obtained in 77% yield. An alternative method for the preparation of compound (4c) has been reported,[9] but our simpler procedure gives a better yield.

Polyphosphoric acid (PPA) [10] and polyphosphoric ester (PPE) [11] were selected as reagents for the ring closure of compounds (4a—d). The cyclization of the diester (4a) with PPE did not occur at 100°; however at 120° the quinoline (5a) was obtained in 78% yield.

Treatment of the nitrile (4b) under the same conditions afforded two products with m.p.s 216—218 and 160—162°. Both the ethoxycarbonyl and the cyano-group of (4b) could conceivably take part in the cyclization reaction. 1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxoquinoline-3-carbonitrile and ethyl 1-ethyl-1,4-dihydro-6,7-methylenedioxy-4-iminoquinoline-3-carboxylate are thus possible products. However, the i.r. spectra of the two products lacked an absorption band of a cyano-group and showed an ester carbonyl band (1690 cm^{-1}). The u.v. spectra showed absorption maxima at 343 and 358 nm. These bands exhibit a bathochromic shift relative to the corresponding one of compound (5a) suggesting the presence of a 4-imino- rather than a 4-oxo-group. The n.m.r. spectra of the compound, m.p. 216—218°, showed signals attributable to one *N*-ethyl and one *O*-ethyl group, while that of the lower-melting compound indicated the presence of two *N*-ethyl and one *O*-ethyl groups. From these data and the elementary analyses, the structure (5b) was assigned to the higher-melting and (5c) to the lower-melting compound. The predominant formation of compounds (5b) and (5c) is explained by the *cis* arrangement of the cyano-group to the anilino-group being thermodynamically [8] preferred and also by the cyano-group being more

TABLE 1

Cyclization of acrylic acid derivatives with PPE

Reactant	Product	Yield (%)
(4a)	(5a)	78
(4b)	(5b)	52·5
	(5c)	10·5
(4c)	(5d)	49
	(5e)	Trace
(4d)	(5f)	Trace
(7a)	(8a)	68
(7b)	(8b)	38·6
(7c)	(8c)	0
(7d)	(8d) *	7·9
	(9)	6·5

* Obtained by thermal cyclization of ketone (7d).

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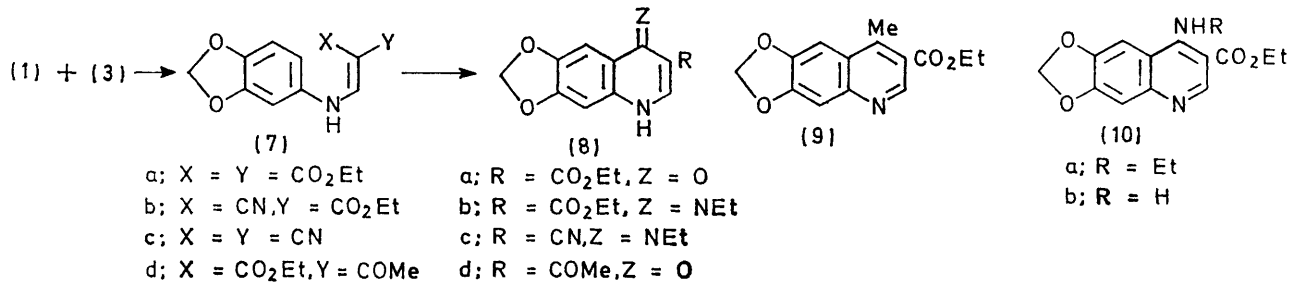
liable to involvement in the cyclizations than the ester group. Alkylation [12] by PPE at elevated temperature is well known. Compound (5c) is thus presumably formed by the ethylation of the initial product (5b). This is the first report of cyclization involving a cyano-group with PPE.

Compound (4c) was cyclized similarly (100°, 7 h) to give the quinoline (5d) (49%) as the main product. Minute amounts of compound (5e) were also isolated from the mother liquors of recrystallization of (5d). The low yield of compound (5d) was due to the formation of by-products. Semiquantitative analysis of the reaction mixture by u.v. spectrometry revealed >80% completion of the cyclization. The cyclization of the ketone (4d); yielded only a trace of the quinoline (5f), the structure of which was assigned by comparison with the product from the ethylation of the ketone (8d). Finally, the quinolines (5a—f) were transformed into oxolinic acid (6) in good yield by acidic and alkaline hydrolysis, or by a haloform reaction.

The cyclization of the acrylic acid derivatives (7) with PPE was also investigated. The reaction proceeded coupling between the exocyclic nitrogen proton and the methylene protons of the ethyl group in the n.m.r. spectrum and the lack of an absorption maximum characteristic of a 4-iminoquinonoid structure in the u.v. spectrum. Compound (7b) yielded the quinoline (9) in 6·5% yield only.

The use of PPA was successful only in the cyclizations * of (4a). PPA is less effective in these reactions, as the acrylic acid derivatives (4) and (7) are readily decomposed by its protic character, and also because the acid is inefficient in activating the cyano-group.

The data in Table 1 indicate that PPE is a better reagent than PPA for the cyclization of compounds (4) and (7) and that the PPE method is complementary to the Conrad–Limpach procedure [3,4] for the synthesis of 1-alkyl-1,4-dihydro-4-oxoquinolines.



similarly to afford the expected products, though some differences due to the fact that the aniline nitrogen atom was no longer alkylated were observed. Treatment of compound (7b) with PPE at 120—140° for 4 h afforded ethyl 4-ethylamino-6,7-methylenedioxyquinoline-3-carboxylate(10a) in 38% yield. The non-alkylated product (10b) was not isolated. The 4-aminoquinoline structure of (10) was supported by the observation of

TABLE 2

Condensation products of the reaction of methylenedioxyaniline (1) with acrylic acid derivatives

Product	M.p. (°C)	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Calc. (%) C	Calc. (%) H	Calc. (%) N
(7b)	146—147 [a]	90	60·0	4·65	10·75	60·2	4·55	11·15
(7c)	235—236 [a]	95	61·95	3·3	19·7	62·1	3·35	19·85
(7d)	94—97 [b]	98	60·65	5·45	5·05	60·85	5·5	5·25

[a] From AcOEt. [b] From MeOH.

spectra were determined on a Hitachi–Perkin-Elmer R-20A at 60 MHz for deuteriochloroform solutions with tetramethylsilane as internal reference.

N-Ethyl-3,4-methylenedioxyaniline (2).—3,4-Methylenedioxyaniline [13] (1) (200 g, 1·46 mol), acetaldehyde (72·3 g), sodium acetate trihydrate (30 g), and Raney nickel (140 ml of methanol slurry) in methanol (3·8 l) were stirred under hydrogen. After 4 h a further portion of acetaldehyde (8·0 g) was added and the reduction was continued to completion (t.l.c.). The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residual oil was distilled *in vacuo* to afford the product (2) (221 g, 91·8%), b.p. 121—122° at 4 mmHg, as an oil. G.l.c. showed the presence of *NN*-diethyl-3,4-methylenedioxyaniline (2%). The *picrate* gave yellow prisms, m.p. 156—158° (from ethanol) (Found: C, 46·05; H, 3·7; N, 14·4. $C_{15}H_{14}N_4O_9$ requires C, 45·7; H, 3·6; N, 14·2%).

Condensation Reactions.—General procedure. Equimolar amounts of 3,4-methylenedioxyaniline (1) and a 1-substituted 2-ethoxy-acrylate [14-17] (or -acrylonitrile) (3) in benzene were refluxed for 30 min. After evaporation of the solvent the residue was triturated with light petroleum and

* While we were investigating this reaction, the use of PPA in the synthesis of 4-oxoquinolines was reported (Jap. Pat. 44–10549, 1969).

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crystals were collected and used for the next reaction without further purification. M.p.s, yields, and analytical data are in Table 2.

The acrylates (4). Compound (2) (1·65 g, 10 mmol) and the ester (3d) (2·05 g, 11 mmol) in tetrahydrofuran (10 ml) were heated under reflux for 2 h. The solution was concentrated under reduced pressure and the residue which crystallized on cooling was recrystallized from ether–ethanol to afford *ethyl* 1-*acetyl*-2-(N-*ethyl*-3,4-*methylenedioxyanilino*)-*acrylate* (4d) (2·69 g, 88%) as prisms, m.p. 92—93°, $\nu_{max.}$ 1690, 1640, 1546, and 1481 cm^{-1} (Found: C, 63·1; H, 6·35; N, 4·55. $C_{16}H_{19}NO_5$ requires C, 62·95; H, 6·25; N, 4·6%). Similarly prepared were *ethyl* 1-*ethoxycarbonyl*-2-(N-*ethyl*-3,4-*methylenedioxyanilino*)*acrylate* (4a) (in refluxing dioxan for 6 h with Triton B as catalyst), b.p. 195—197° at 0·07 mmHg, $\nu_{max.}$ 2970, 2880, 1710, 1690, 1590, and 1485 cm^{-1} (Found: C, 60·4; H, 6·4; N, 3·95. $C_{17}H_{21}NO_6$ requires C, 60·9; H, 6·3; N, 4·2%); *ethyl* 1-*cyano*-2-(N-*ethyl*-3,4-*methylenedioxyanilino*)*acrylate* (4b) (in refluxing dioxan for 7 h with Triton B as catalyst), m.p. 79—83°, $\nu_{max.}$ 2190, 1688, 1585, and 1480 cm^{-1}, τ 2·1 (1H, s), 3·1—3·4 (3H, m), 3·95 (2H, s), 5·26 (4H, q, J 7·2 Hz), and 8·7 (6H, t, J 7·2 Hz) (Found: C, 62·6; H, 5·65; N, 9·8. $C_{15}H_{16}N_2O_4$ requires C, 62·5; H, 5·6; N, 9·7%); 1-*cyano*-2-(N-*ethyl*-3,4-*methylenedioxyanilino*)*acrylonitrile* (4c) (in tetrahydrofuran at 20—25° for 20 h with zinc chloride as catalyst), m.p. 103—107°, $\nu_{max.}$ 2180, 1610—1600, 1257, 1038, and 931 cm^{-1} (Found: C, 65·0; H, 4·65; N, 17·6. $C_{13}H_{11}N_3O_2$ requires C, 64·7; H, 4·60; N, 17·4%).

Cyclization Reactions.—PPE method. The ester (4a) (2·0 g) and PPE (8·0 g) were heated at 110—120° for 1 h. The cooled mixture was poured into ice–water (80 ml) and neutralized with sodium hydrogen carbonate. The precipitate was collected and crystallized from benzene to yield the dihydroquinoline (5a) (1·36 g, 78·8%), m.p. 174—176°, $\nu_{max.}$ 1720, 1689, 1635, 1600, and 1577 cm^{-1}, identical with an authentic sample.[7]

Similarly the ester (4b) (2·0 g) and PPE (10 g) were heated at 120—130° for 5 h. The cooled mixture was poured into ice–water (100 ml), made alkaline with potassium carbonate, and extracted with chloroform. The chloroform layer was washed with water and dried (K_2CO_3). Evaporation of the solvent gave a yellow solid which on crystallization afforded *ethyl* 1-*ethyl*-4-*ethylimino*-1,4-*dihydro*-6,7-*methylenedioxyquinoline*-3-*carboxylate* (5c) (0·23 g, 10·5%) as pale yellow leaflets m.p. 160—162° (from ether–ethyl acetate), $\nu_{max.}$ 1690, 1635, 1587, and 1505 cm^{-1}, $\lambda_{max.}$ 229 (log ε 4·24), 271·5 (4·55), 285·2 (4·51), 328 (4·01), 343 (4·04), and 358 nm (4·03), τ 2·3 (1H, s), 2·42 (1H, s), 3·48 (1H, s), 4·08 (2H, s), 5·77 (2H, q, J 7·2 Hz), 6·15 (2H, q, J 7·2 Hz), 6·85 (2H, q, J 7·2 Hz), and 8·5—8·85 (9H, m) (Found: C, 64·55; H, 6·45; N, 8·75. $C_{17}H_{20}N_2O_4$ requires C, 64·55; H, 6·35; N, 8·85%). The aqueous layer was made alkaline with aqueous 10% sodium hydroxide (40 ml) and kept at room temperature overnight. The solution was extracted with chloroform (200 ml) and the chloroform layer was dried (K_2CO_3). Evaporation of the solvent gave a white solid which on crystallization afforded *ethyl* 1-*ethyl*-1,4-*dihydro*-4-*imino*-6,7-*methylenedioxyquinoline*-3-*carboxylate* (5b) (1·05 g, 52·5%) as needles, m.p. 216—218° (decomp.) (from isopropyl alcohol), $\nu_{max.}$ 3420, 3280, 1640, 1580, 1560, 1505, 1203, and 1028 cm^{-1}, $\lambda_{max.}$ 229 (log ε 4·12), 271 (4·42), 281 (4·48), 342 (4·08), and 357 nm (4·12), τ[$(CD_3)_2SO$] 1·23 (1H, s), 2·22 (1H, s), 2·41 (1H, s), 3·73 (2H, s), 5·5 (2H, q, J 7·2 Hz), 6·15 (2H, q, J 7·2 Hz), and 8·66 (6H, t, J 7·2 Hz) (Found: C, 58·75; H, 5·65; N, 9·1. $C_{15}H_{16}N_2O_4,H_2O$ requires C, 58·8; H, 5·9; N, 9·15%).

The nitrile (4c) was treated similarly with PPE (100°, 7h) to give 1-*ethyl*-4-*ethylimino*-1,4-*dihydro*-6,7-*methylenedioxy*-3-*carbonitrile* (5d) (49%) as yellow leaflets, m.p. 203—207° (from ethanol), $\nu_{max.}$ 2190, 1633, 1590, 1273, 1200, and 1045 cm^{-1}, $\lambda_{max.}$ (H_2O) 227·5 (log ε 4·25), 270 (4·49), 339 (4·11), and 355 nm (4·12), τ 2·15 (1H, s), 2·70 (1H, s), 3·4 (1H, s), 4·0 (2H, s), 6·10 (2H, q, J 7·2 Hz), 6·13 (2H, q, J 7·2 Hz), 8·55 (3H, t, J 7·2 Hz), and 8·65 (3H, t, J 7·2 Hz) (Found: C, 67·25; H, 5·7; N, 15·75. $C_{15}H_{15}N_3O_2$ requires C, 66·9; H, 5·6; N, 15·6%).

In one experiment, fractional recrystallization of the crude product gave a small amount (1·3%) of *ethyl* 1,N(3′)-*diethyl*-4-*ethylimino*-1,4-*dihydro*-6,7-*methylenedioxyquinoline*-3-*carboximidate* (5e), prisms, m.p. 133—134° (from isopropyl alcohol) (Found: C, 66·25; H, 7·4; N, 12·4. $C_{19}H_{25}N_3O_3$ requires C, 66·45; H, 7·35; N, 12·25%).

The ketone (4d) on treatment with PPE at 100—105° for 1 h afforded the ketone (5f) as leaflets, identical with an authentic sample prepared as described later.

The ester (7b) on treatment with PPE at 120—130° for 4 h afforded *ethyl* 4-*ethylamino*-6,7-*methylenedioxyquinoline*-3-*carboxylate* (8b) (38·6%) as pale yellow needles, m.p. 123—125° (from ether), $\nu_{max.}$ 3100—3300, 1660, 1612, 1598, 1531, and 1500 cm^{-1}, $\lambda_{max.}$ 227 (log ε 4·13), 268 (4·52), 282·5 (4·49), 305 (4·07), 314 (3·73), 350 (3·59), and 363 nm (3·56), τ 0·95—1·35 (1H), 1·0 (1H, s), 2·53 (1H, s), 2·77 (1H, s), 3·93 (2H, s), 5·62 (2H, q, J 7·2 Hz), 6·32 (2H, d, q, J 7·2 and 1·5 Hz), 8·58 (3H, t, J 7·2 Hz), and 8·62 (3H, t, J 7·2 Hz) (Found: C, 62·8; H, 5·65; N, 9·76. $C_{15}H_{16}N_2O_4$ requires C, 62·5; H, 5·6; N, 9·7%).

The ketone (7d) and PPE were heated at 110° for 15 min to afford *ethyl* 4-*methyl*-6,7-*methylenedioxyquinoline*-3-*carboxylate* (9) (6·5%) as prisms, m.p. 155—157° (from isopropyl alcohol), τ 1·55 (1H, s), 2·75 (1H, s), 3·0 (1H, s), 3·92 (2H, s), 5·6 (2H, q, J 7·2 Hz), 7·1 (3H, s), and 8·55 (3H, t, J 7·2 Hz) (Found: C, 64·55; H, 5·05; N, 5·4. $C_{14}H_{13}NO_4$ requires C, 64·85; H, 5·05; N, 5·4%).

PPA method. The ester (4a) and PPA were heated at 120—130° for 30 min. Work-up as in the PPE method gave the ester (5a) (64%), m.p. 172—174°.

Thermal Cyclization of the Ketone (7d).—The ketone (7d) (5·0 g) and diphenyl ether (75 g) were heated under reflux for 20 min. After cooling, solid which had formed was collected, washed with n-hexane, and crystallized to give 3-*acetyl*-1,4-*dihydro*-6,7-*methylenedioxy*-4-*oxoquinoline* (8d) (3·3 g, 79%) as pale yellow needles, m.p. 290° (decomp.) (from dimethylformamide) (Found: C, 62·75; H, 3·95; N, 6·25. $C_{12}H_9NO_4$ requires C, 62·35; H, 3·9; N, 6·05%).

3-*Acetyl*-1-*ethyl*-1,4-*dihydro*-6,7-*methylenedioxy*-4-*oxoquinoline* (5f).—To the ketone (8d) (1·38 g, 6 mmol) in dimethylformamide (25 ml), sodium hydride (52·9% in mineral oil, 0·55 g, 12 mmol) was added in portion and the solution was stirred at room temperature for 30 min. Ethyl iodide (1·56 g, 10 mmol) in dimethylformamide (5 ml) was then added at 70° over 30 min, and the mixture was stirred for a further 3·5 h. More ethyl iodide (0·75 g, 5 mmol) was added after 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with water (*ca.* 30 ml) and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown solid (1·35 g), which afforded the *ketone* (5f) (1·0 g, 64·5%), m.p. 218—220° (decomp.) (from ethanol) as needles, $\nu_{max.}$ 1658, 1630, 1575, 1555, and

1500 cm^{-1}, $\tau(CDCl_3)$ 1·61 (1H, s), 2·15 (1H, s), 3·1 (1H, s), 3·83 (2H, s), 5·77 (2H, q, J 7·2 Hz), 7·21 (3H, s), and 8·45 (3H, t, J 7·2 Hz) (Found: C, 64·6; H, 5·0; N, 5·6. $C_{14}H_{13}NO_4$ requires C, 64·85; H, 5·05; N, 5·4%). The product was identical with that from the cyclization of the ketone (4d).

Transformation of Ketone (5f) *to Oxolinic Acid* (6).—To dioxan (5 ml) and freshly prepared sodium hypochlorite solution (5 g, 5·79 mmol) was added powdered ketone (5f) (5 g, 1·93 mmol) with stirring at room temperature. The mixture became clear in 5 min and after 30 min was washed with chloroform to remove unchanged material. The aqueous solution was made acidic with 10% hydrochloric acid and the precipitate was collected. Crystallization gave oxolinic acid (350 mg, 69·5%) as prisms, m.p. 298—302° (decomp.) (from dimethylformamide), identical with an authentic sample.[7]

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