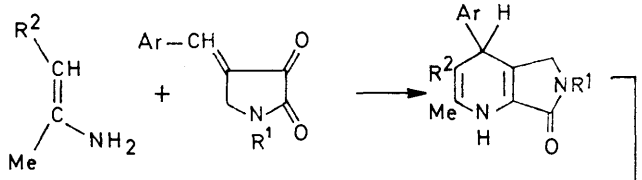
# Reactions of 4-Arylmethylenepyrrolidine-2,3-diones. Synthesis of Pyrrolo[3,4-*b*]-pyridines and -quinolines [1]

By R. Madhav, Mellon Institute, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213, U.S.A.

4-Arylmethylenepyrrolidine-2,3-diones (1) condense with ethyl β-aminocrotonoate or with 4-aminopent-3-en-2-one to give adducts which can be dehydrogenated to afford pyrrolo[3,4-*b*]pyridines. *N*-Phenacylpyridinium salts also react with the pyrrolidinediones (1), to form 2,4-diarylpyrrolo[3,4-*b*]pyridines. In addition, *o*-nitrobenzylidenepyrrolidine-2,3-diones undergo reductive cyclization to give pyrrolo[3,4-*b*]quinolines.

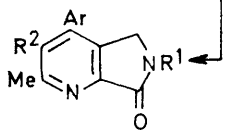
THE ready conversion of pyrrolidine-2,3-diones (2) into their 4-arylmethylene derivatives (1) has been reported.[2] These derivatives can undergo nucleophilic addition to the αβ-unsaturated ketonic function, giving bicyclic and polycyclic systems incorporating a pyrroline ring fused across the 3- and 4-positions. For example, pyrrolo[3,4-*d*]pyrimidines have been obtained by the reaction of the benzylidene compounds with guanidine.[3] We have been investigating the versatility of these compounds as intermediates for the preparation of heterocycles,[1] and now report a convenient synthesis of



(2) $R^2 = CO_2Et$ (1) (4) $R^2 = CO_2Et$

(3) $R^2$ = MeCO (5) $R^2$ = MeCO

| | Ar | $R^1$ |
|---|---|---|
| a; | Ph | $[CH_2]_5CH$ |
| b; | 4-MeO·$C_6H_4$ | $[CH_2]_5CH$ |
| c; | 3-$O_2N$·$C_6H_4$ | $[CH_2]_5CH$ |
| d; | Ph | $Bu^t$ |
| e; | Ph | $PhCH_2$ |
| f; | Ph | $MeO_2C·[CH_2]_2$ |
| g; | 2-$O_2N$·$C_6H_4$ | $[CH_2]_5CH$ |
| h; | 2-$O_2N$·$C_6H_4$ | $Ph[CH_2]_2$ |

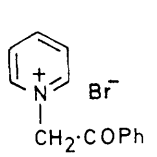


(6) $R^2 = CO_2Et$

(7) $R^2$ = MeCO

pyrrolo[3,4-*b*]-pyridines and -quinolines. The only reported route to pyrrolo[3,4-*b*]pyridines starts from quinolinic acids.[4]

The arylmethylene derivatives (1) were obtained by the acid-catalysed aldol condensation of aromatic aldehydes with 1-substituted pyrrolidine-2,3-diones, which can be prepared by hydrolysis and decarboxylation of the enol forms of 1-substituted 4-alkoxycarbonylpyrrolidine-2,3-diones.[5] Two general methods were employed for the construction of pyrrolo[3,4-*b*]pyridines.



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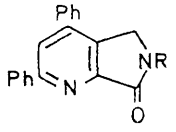


(9) a; $R = [CH_2]_5CH$

b; $R = PhCH_2$

c; $R = MeO_2C·[CH_2]_2$

The arylmethylene derivatives (1a—e) were condensed with ethyl β-aminocrotonate (2) or [for (1a)] with 4-aminopent-3-en-2-one (3) (derived from acetylacetone) to afford the non-aromatic adducts (4a—e) and (5a). The adducts were not purified but could be treated with bromine to give the pyrrolo[3,4-*b*]pyridines (6a—e) and (7a).

The other route made use of *N*-phenacylpyridinium bromide (8) as the activated methylene component. Its reaction with the arylmethylene derivatives (1a, e, and f) in the presence of ammonium acetate occurred smoothly to give the pyrrolo[3,4-*b*]pyridines (9a—c). The carbonyl group of (9a) could be reduced with lithium aluminium hydride.

The *o*-nitrobenzylidene derivatives (1g and h) were found to be useful intermediates for the preparation of pyrrolo[3,4-*b*]quinolines (10). Since the recognition that the antileukaemic alkaloid camptothecin contains a pyrrolo[3,4-*b*]quinoline unit, efforts have been directed towards the synthesis of this system. We have previously reported the synthesis of pyrrolo[3,4-*b*]-quinolines from pyrrolidine-2,3-diones and *N*-aryl enamines derived from the enol forms of 4-ethoxycarbonylpyrrolidine-2,3-diones.[6] When the *o*-nitrobenzylidene derivatives (1g and h) were reduced with tin(II) chloride, the products underwent spontaneous

[1] Preliminary communication, R. Madhav, *Synthesis*, 1973, 609.

[2] P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, 1962, **27**, 98; P. L. Southwick, N. Latif, B. M. Fitzgerald, and N. M. Zaczek, *ibid.*, 1966, **31**, 1; P. L. Southwick and R. Madhav, unpublished data.

[3] P. L. Southwick and G. H. Hofmann, *J. Org. Chem.*, 1963, **28**, 1332.

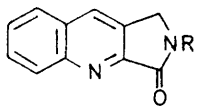
[4] Z. J. Vejdelek, M. Protiva, *Cesk. Farm.*, 1964, **13**, 76 (*Chem. Abs.*, 1964, **10**, 10,662); W. L. F. Armarego, B. A. Milloy, and S. C. Sharma, *J.C.S. Perkin I*, 1972, 2485.

[5] P. L. Southwick and R. T. Crouch, *J. Amer. Chem. Soc.*, 1953, **75**, 3413.

[6] R. Madhav, R. F. Dufresne, and P. L. Southwick, *J. Heterocyclic Chem.*, 1973, **10**, 225; R. Madhav and P. L. Southwick, *ibid.*, 1972, **9**, 443.

ring closure to yield the pyrrolo[3,4-*b*]quinolines (10a and b). Sodium dithionite also brought about the reductive cyclization but in lower yields.

The n.m.r. signal of the olefinic protons of the *o*-nitrobenzylidene derivatives (1g and h) appear at low field



(10) a; R = $[CH_2]_5CH$

b, R = $Ph[CH_2]_2$

(τ 2·5), indicating the *E*-configuration for the double bond.[7] Thus a change in configuration as well as reduction of the nitro-group must be involved in the ring closure reaction. The acidic or basic conditions associated with the reduction step may promote $E \rightleftharpoons Z$ equilibration of the conjugated system.

## EXPERIMENTAL

M.p.s were taken with a Meltemp apparatus and are corrected. I.r. spectra were run for Nujol mulls with a Perkin-Elmer Infracord instrument. $^1H$ N.m.r. spectra were recorded for solutions in $CDCl_3$ or $CDCl_3$–$CF_3 \cdot CO_2H$ (4 : 1) ($Me_4Si$ as internal standard) with a Hitachi–Perkin-Elmer R-20 spectrometer.

1-*Substituted* 4-*Arylmethylenepyrrolidine*-2,3-*diones* (1).—The compounds were prepared by Southwick and Barnas' method.[2]

1-*Cyclohexyl*-4-(o-*nitrobenzylidene*)*pyrrolidine*-2,3-*dione* (1g), obtained from 1-cyclohexyl-4-ethoxycarbonylpyrrolidine-2,3-dione (3·1 g, 0·0125 mol) and *o*-nitrobenzaldehyde (2·8 g, 0·019 mol) (yield 2·0 g, 64·4%), had m.p. 162—164°; $\lambda_{max.}$ 5·78, 5·95, and 6·64 μm; τ ($CDCl_3$) 1·45—2·25 (4H, m, aromatic), 1·7 (1H, s, =CH), 5·5 (2H, s, $CH_2$), 5·4—5·8 (1H, m, methine), and 7·8—8·8 (m, $[CH_2]_5$) (Found: C, 65·2; H, 5·85; N, 8·65. $C_{17}H_{18}N_2O_4$ requires C, 64·95; H, 5·75; N, 8·9%).

4-(o-*Nitrobenzylidene*)-1-*phenethylpyrrolidine*-2,3-*dione* (1h), obtained from 4-ethoxycarbonyl-1-phenethylpyrrolidine-2,3-dione (3·4 g, 0·0125 mol) and *o*-nitrobenzaldehyde (2·8 g, 0·019 mol) (yield 2·1 g, 50·0%), had m.p. 188—189°; $\lambda_{max.}$ 5·77, 5·85, and 6·65 μm; τ ($CDCl_3$–$CF_3 \cdot CO_2H$) 1·50—2·25 (4H, m, aromatic), 1·73 (1H, s, =CH), 2·61 (5H, s, Ph), 5·72 (2H, s, $CH_2$), and 6·05 and 6·83 (4H, t, 2 × $CH_2$) (Found: C, 67·9; H, 4·7; N, 8·1. $C_{19}H_{16}N_2O_4$ requires C, 67·85; H, 4·8; N, 8·35%).

6-*Substituted Ethyl* 4-*Aryl*-6,7-*dihydro*-2-*methyl*-7-*oxo*-5H-*pyrrolo*[3,4-b]*pyridine*-3-*carboxylates* (6).—The 1-substituted 4-arylmethylenepyrrolidine-2,3-dione (1) (0·01 mol), ethyl acetoacetate (0·01 mol), and conc. aqueous ammonia (1 ml) were refluxed in absolute ethanol (10 ml) for 3 h. The mixture was poured into water (250 ml) and the solid which separated was filtered off, washed, and dried. The crude solid (3·0 g) was treated with anhydrous sodium acetate (1·5 g) and bromine (0·8 g, 0·2 mol) in acetic acid (25 ml) under reflux for 2 h. The mixture was diluted with water (300 ml) and the product was filtered off, washed with water, and crystallized from ethanol–water.

The 6-*cyclohexyl*-4-*phenyl derivative* (6a) (yield 63·4%) had m.p. 203—204°; $\lambda_{max.}$ 5·8 and 5·95 μm; τ ($CDCl_3$) 3·0 (5H, s, Ph), 5·95 (1H, m, methine), 6·05 (2H, s, $CH_2$), 6·2 (2H, q, $CH_2 \cdot CH_3$), 7·4 (3H, s, $CH_3$), 8·0—8·9 (10H, m, $[CH_2]_5$), and 9·07 (3H, t, $CH_2 \cdot CH_3$) (Found: C, 72·8; H, 6·8; N, 7·15. $C_{23}H_{26}N_2O_3$ requires C, 73·0; H, 6·95; N, 7·4%). The 6-*cyclohexyl*-4-p-*methoxyphenyl derivative* (6b) (yield 69·2%) had m.p. 183—185°; $\lambda_{max.}$ 5·87 and 6·0 μm; τ ($CDCl_3$) 2·85 (4H, q, aromatic), 5·9 (2H, q, $CH_2 \cdot CH_3$), 6·0 (1H, m, methine), 6·1 (3H, s, $OCH_3$), 6·18 (2H, s, $CH_2$), 7·5 (3H, s, $CH_3$), 7·95—8·65 (10H, m, $[CH_2]_5$), and 8·9 (3H, t, $CH_2 \cdot CH_3$) (Found: C, 70·6; H, 7·2; N, 6·8. $C_{24}H_{28}N_2O_4$ requires C, 70·55; H, 6·9; N, 6·9%). The 6-*cyclohexyl*-4-m-*nitrophenyl derivative* (6c) (yield 74·3%) had m.p. 231—232°; $\lambda_{max.}$ 5·85, 5·95, and 6·63 ($NO_2$) μm; τ ($CDCl_3$) 2·45—3·22 (4H, m, aromatic), 6·0 (1H, m, methine), 6·3 (2H, q, $CH_2 \cdot CH_3$), 6·65 (4H, d, 2 × $CH_2$), 7·65 (3H, s, $CH_3$), 8·1—8·8 (10H, m, $[CH_2]_5$), and 8·95 (3H, t, $CH_2 \cdot CH_3$) (Found: C, 65·5; H, 6·25; N, 9·65. $C_{23}H_{25}N_3O_5$ requires C, 65·25; H, 5·95; N, 9·9%). The 6-*t-butyl*-4-*phenyl derivative* (6d) (yield 78·2%) had m.p. 218—220°; $\lambda_{max.}$ 5·87 and 5·95 μm; τ ($CDCl_3$) 2·45 (5H, s, Ph), 5·85 (2H, q, $CH_2 \cdot CH_3$), 6·15 (2H, s, $CH_2$), 7·4 (3H, s, $CH_3$), 8·5 (9H, m, $Bu^t$), and 8·85 (3H, t, $CH_2 \cdot CH_3$) (Found: C, 71·75; H, 7·05; N, 7·85. $C_{21}H_{24}N_2O_3$ requires C, 71·55; H, 6·85; N, 7·95%). The 6-*benzyl*-4-*phenyl derivative* (6e) (yield 93·4%) had m.p. 174—175°; $\lambda_{max.}$ 5·88 and 6·0 μm; τ ($CDCl_3$) 3·2 (10H, s, aromatic), 5·7 and 6·6 (4H, two s, 2 × $CH_2$), 6·25 (2H, q, $CH_2 \cdot CH_3$), 7·7 (3H, s, $CH_3$), and 9·0 (3H, t, $CH_2 \cdot CH_3$) (Found: C, 74·4; H, 5·95; N, 7·1. $C_{24}H_{22}N_2O_3$ requires C, 74·6; H, 5·75; N, 7·1%).

3-*Acetyl*-6-*cyclohexyl*-5,6-*dihydro*-2-*methyl*-4-*phenylpyrrolo*-[3,4-b]*pyridin*-7-*one* (7a), obtained by the same general procedure as described for (6a) (yield 57·3%), had m.p. 228—230°; $\lambda_{max.}$ 5·92 and 5·95 μm; τ ($CDCl_3$) 2·7 (5H, s, Ph), 6·0 (1H, m, methine), 6·3 (2H, s, $CH_2$), 7·5 (3H, s, $CH_3$), 7·92 (3H, s, $CH_3$), and 8·0—8·85 (10H, m, $[CH_2]_5$) (Found: C, 76·0; H, 7·2; N, 7·85. $C_{22}H_{24}N_2O_2$ requires C, 75·85; H, 6·95; N, 8·05%).

6-*Substituted* 5,6-*Dihydro*-2,4-*diphenylpyrrolo*[3,4-b]-*pyridin*-7-*ones* (9).—The 1-substituted 4-benzylidenepyrrolidine-2,3-dione (1) (0·005 mol) *N*-phenacylpyridinium bromide (8) (0·005 mol), and ammonium acetate (1·0 g) were refluxed in 20 : 1 ethanol–acetic acid (21 ml) for 3 h. The mixture was poured into water (250 ml) and extracted with ethyl acetate (3 × 50 ml). The extract was washed with water, dried ($Na_2SO_4$), and evaporated. The crude product was crystallized from ethyl acetate–petroleum (b.p. 30—60°) or ethanol–water.

The 6-*cyclohexyl derivative* (9a) (yield 61·2%) had m.p. 235—236°; $\lambda_{max.}$ 5·96 μm; τ ($CDCl_3$) 1·55 (1H, m, aromatic), 2·0—2·35 (10H, m, aromatic), 5·35 (2H, s, $CH_2$), 5·5 (1H, m, methine), and 7·8—8·85 (10H, m, $[CH_2]_5$) (Found: C, 81·6; H, 6·3; N, 7·45. $C_{25}H_{24}N_2O$ requires C, 81·5; H, 6·55; N, 7·6%). The 6-*benzyl derivative* (9b) (yield 49·5%) had m.p. 182—183°; $\lambda_{max.}$ 5·95 μm; τ ($CDCl_3$) 1·62 (1H, m, aromatic), 2·0—2·35 (15H, m, aromatic), 5·15 (2H, s, $CH_2$), and 5·8 (2H, s, $CH_2$) (Found: C, 79·15; H, 5·6; N, 7·1. $C_{26}H_{22}N_2O_2,H_2O$ requires C, 79·4; H, 5·65; N, 6·9%). The 6-(2-*methoxycarbonylethyl*) *derivative* (9c) (yield 41·1%) had m.p. 140—141°; $\lambda_{max.}$ 5·8 and 5·95 μm; τ ($CDCl_3$) 1·6

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(1H, m, aromatic), 2·0—2·5 (10H, m, aromatic), 5·65 (2H, s, $CH_2$), 6·08 (2H, m, $CH_2$), 6·2 (3H, s, $CH_3$), and 7·15 (2H, m, $CH_2$) (Found: C, 74·0; H, 5·3; N, 7·7. $C_{23}H_{20}N_2O_3$ requires C, 74·15; H, 5·4; N, 7·5%).

*6-Cyclohexyl-5,6-dihydro-2,4-diphenylpyrrolo*[3,4-b]*pyridin-7-one*.—A suspension of (9a) (0·9 g) was reduced with lithium aluminum hydride in dry tetrahydrofuran (100 ml) under nitrogen for 20 h. The product (0·3 g), a viscous oil, was characterized as its *picrate*, m.p. 189—190° (from ethanol) (Found: C, 63·55; H, 5·0; N, 11·7. $C_{31}H_{29}N_5O_7$ requires C, 63·8; H, 5·0; N, 12·0%).

*1-Substituted 1,2-Dihydropyrrolo*[3,4-b]*quinolin-3-ones* (10).—(a) By *reduction with tin*(II) *chloride*. To tin(II) chloride dihydrate (1·5 g) dissolved in conc. hydrochloric acid (15 ml) was added compound (1g) or (1h) (0·5 g). The solution was stirred at ambient temperature for 24—40 h, then cooled to 0° and slowly neutralized with aqueous ammonia. The precipitate was filtered off, dried, mixed with sand, and extracted with chloroform (Soxhlet) for 2 days. The extract was evaporated and the residue was crystallized from ethanol to give a white crystalline solid.

The *1-cyclohexyl derivative* (10a) (yield 0·2 g, 44·2%) had m.p. 311—313°; $\lambda_{max.}$ 6·0 μm; τ ($CDCl_3$–$CF_3$·$CO_2H$) 1·1—2·1 (5H, m, aromatic), 5·0 (2H, s, $CH_2$), 5·4—5·8 (1H, m, methine), and 7·8—8·8 (10H, m, $[CH_2]_5$) (Found: C, 72·15; H, 6·8; N, 9·85. $C_{17}H_{18}N_2O,H_2O$ requires C, 72·5; H, 6·5; N, 9·85%). The *1-phenethyl derivative* (10b) (yield 51·4%) had m.p. 224—225°; $\lambda_{max.}$ 5·95 μm; τ ($CDCl_3$–$CF_3$·$CO_2H$) 0·65—1·9 (5H, m, aromatic), 2·1 (5H, s, Ph), 5·1 (2H, s, $CH_2$), and 5·75 and 6·8 (4H, t, 2 × $CH_2$) (Found: C, 79·0; H, 5·65; N, 9·7. $C_{19}H_{16}N_2O$ requires C, 79·15; H, 5·6; N, 9·7%).

(b) *By reduction with sodium dithionite*. Compound (1g) (0·2 g) in hot ethanol (20 ml) was treated with aqueous sodium dithionite (2 g in 4 ml) for 1 h. The solution was diluted with water and extracted with ethyl acetate, and the extract was dried ($Na_2SO_4$) and evaporated. Crystallization of the residue from ethanol gave compound (10a) (0·03 g, 16·6%), identified by mixed m.p.

I thank Dr. P. L. Southwick for his interest in this work.

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