Preparation of 1,2-Dihydro-3-oxo-3*H*-pyrrolo[3,4-*b*]quinoline Derivatives from 2,3-Dioxopyrrolidines

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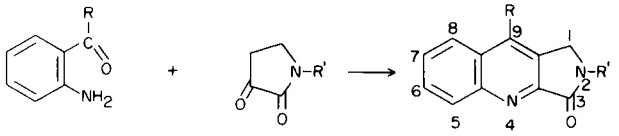
Received October 8, 1971

The preparation of compounds containing the pyrrolo[3,4-*b*]quinoline system had received no attention until rather recently. Two derivatives were described in 1965 by Kempter and Hirschberg (1), but active interest in the series developed slightly later (1966) with the recognition that the alkaloid camptothecin incorporates the pyrrolo[3,4-*b*]quinoline structure (2). Reports of the antileukemic and antitumor activity of camptothecin have stimulated much activity directed toward the synthesis of camptothecin (3), any complete scheme for which requires at one stage the construction of the pyrrolo[3,4-*b*]quinoline moiety.

We have found that 2,3-dioxopyrrolidines (II) condenses smoothly with *o*-aminoaryl ketones (I) (*o*-aminoacetophenone, *o*-aminobenzophenone, or *o*-aminobenzoylformic acid derived *in situ* from isatin) to yield 1,2-dihydro-3-oxo-3*H*-pyrrolo[3,4-*b*]quinoline derivatives (III). In the case of *o*-aminoacetophenone and *o*-aminobenzophenone the condensation occurred in high yield (see Table I) in refluxing acetic acid containing a trace of sulfuric acid (conditions of the Friedlander quinoline



I II III

synthesis) (4). The condensation involving isatin, from which the yields were lower, but still quite satisfactory, were conducted in refluxing ethanolic potassium hydroxide, under the usual conditions of the Pfitzinger reaction (4). Many 1-substituted-2,3-dioxopyrrolidines would be accessible for use in this type of synthesis (5).

EXPERIMENTAL (6,7)

Results obtained in the preparation of six compounds by use of these condensation procedures are recorded in the table.

Method A - Condensations with *o*-Aminoaryl Ketones.

A mixture of 1-substituted 2,3-dioxopyrrolidine (5) (0.01 mole) and *o*-aminobenzophenone (6) or *o*-aminoacetophenone (6) (0.01 mole) was refluxed in glacial acetic acid (10 ml.) containing 0.1 ml. of concentrated sulfuric acid for a period of 3 hours. The dark-brown solution was cooled, and basified with aqueous ammonium hydroxide. The precipitated solid was collected by filtration, washed with water, and crystallized from ethanol.

Method B - Condensations with Isatin.

A mixture of 1-substituted 2,3-dioxopyrrolidine (5) (0.01 mole), isatin (6) (0.0103 mole) and powdered potassium hydroxide (0.035 mole) was refluxed in 95% ethanol (8 ml.) for 12 hours. The reaction mixture, which contained a greyish-white suspended solid, was poured into ice-water (100 ml.). The mixture was treated with Norit while hot and filtered. The light tan-colored filtrate was cooled and acidified with 50% aqueous acetic acid to give the solid product, which was crystallized from ethanol.

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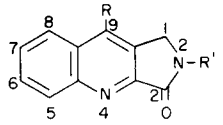
(4) R. H. Manske, *Chem. Rev.*, **30**, 124 (1942); F. W. Bergstrom, *ibid.*, **35**, 151 (1944).

(5) The 1-substituted-2,3-dioxopyrrolidines used in the present investigation are described in the following two references: (a) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, 21, 1087 (1956); P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, 75, 3413 (1953).

(6) Used as obtained from the Aldrich Chemical Company, Inc.

(7) Microanalyses are by M-H-W Laboratories, Garden City, Michigan. Melting points were determined with a Mel-Temp apparatus in capillary tubes and are corrected.

TABLE I



R	R′	Method	Yield %	M.p., °C	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5-	cyclo C_6H_{11}	A	95.5	227-228	$C_{23}H_{22}ON_2$ (a)	80.67	6.48	8.18	80.69	6.33	8.09
C_6H_5	-CH_2-C_6H_5	A	100.0	329-330	$C_{24}H_{18}ON_2$ (b)	82.26	5.18	8.00	82.44	5.14	7.86
CH_3	cyclo C_6H_{11}	A	99.9	200-201	$C_{18}H_{20}ON_2$ (c)	77.11	7.19	9.99	77.23	7.18	9.99
CH_3	-CH_2-C_6H_5	A	100.0	199-200	$C_{19}H_{16}ON_2$ (d)	79.14	5.59	9.72	78.96	5.70	9.64
-CO_2H	cyclo C_6H_{11}	B	71.3	>360	$C_{18}H_{18}O_3N_2$ (e)	69.66	5.85	9.03	69.48	5.78	8.85
-CO_2H	-CH_2-C_6H_5	B	84.3	279-280	$C_{19}H_{14}O_3N_2$ (f)	71.69	4.43	8.80	71.64	4.31	8.65

(a) Ir (Nujol) μ 5.89, 6.00, 12.99, 13.16, 14.12, 14.31; nmr (deuteriochloroform + Trifluoroacetic acid (TFA), 3:1) τ 1.50-2.01 (m, 4, quinoline), 2.38 (s, 5, phenyl at position 9), 5.41 (s, 2, methylene at position 1), 5.70 (m, 1, methine of cyclohexyl), 7.91-8.80 (m, 10, cyclohexyl); (b) Ir (Nujol) μ 5.91, 6.00, 12.91, 13.07, 13.25, 14.17, 14.37; nmr (deuteriochloroform + TFA, 3:1), τ 1.60-2.51 (m, 4, quinoline), 2.55 (s, 5, phenyl at position 9), 2.76 (s, 5, C_6H_5·CH_2 group), 5.18 (s, 2, methylene at position 1), 5.8 (s, 2, benzylic methylene); (c) Ir (Nujol) μ 5.85, 6.00, 13.00, 13.15, 13.70, 14.15; nmr (deuteriochloroform + TFA, 3:1) τ 1.65-2.10 (m, 4, quinoline), 5.31 (s, 2, methylene at position 1), 5.80 (m, 1, methine of cyclohexyl), 7.10 (s, 3, methyl at position 9), 7.90-8.80 (m, 10, cyclohexyl); (d) Ir (Nujol) μ 5.85, 6.00, 13.00, 13.15, 13.70, 14.15; nmr (deuteriochloroform) τ 1.61-2.20 (m, 4, quinoline), 2.60 (s, 5, C_6H_5·CH_2 group), 5.05 (s, 2, methylene at position 1), 5.79 (s, 2, benzylic methylene), 7.44 (s, 3, methyl at position 9); (e) Ir (Nujol) μ 5.80, 5.92, 5.98, 13.00, 13.57, 14.00, 14.50; nmr (deuteriochloroform + TFA, 3:1) τ 0.81-1.65 (m, 4, quinoline), 4.81 (s, 2, methylene at position 1), 5.61 (m, 1, methine of cyclohexyl), 7.85-8.80 (m, 10, cyclohexyl); (f) Ir (Nujol) μ 5.80, 5.91, 6.00, 12.95, 13.51, 13.65, 14.25; nmr (deuteriochloroform + TFA, 3:1) τ 0.81-1.70 (m, 4, quinoline), 2.59 (s, 5, C_6H_5·CH_2 group), 4.82 (s, 2, methylene at position 1), 4.98 (s, 2, benzylic methylene).