Pakistan J. Pharm. Sci. Vol.2(No.2), 1989.

THE SYNTHESIS OF 4-[(2-HYDROXY-4-QUINOLYL) METHYLI-3,5-PYRAZOLIDINEDIONES AND RELATED PRODUCTS

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ABSTRACT

In the present work, the s sis of 4-[(2-HydroxyAyuinoyl)mcthyl]-3,5-pyrazo-lidinediones and related compounds has been described.

Introduction

Many quinoline derivatives have found useful applications as chemotherapeutic agents (Burckhalter and co-workers, 1948). On the other hand, several 5-pyrazolones and 3,5-pyrazolidinediones possess marked antiin0ammatory activity (Foye, 1974) and uricosurie properties (Eid, Kira and Fahmy, 1978). Also certain isoxazoles (Katritzky, 1966) and barbituric acid derivatives (Skoda *et. al,* 1962) have been shown to interfere with nucleic acid biosynthesis.

In the view of these data's twelve new carbostrils incorporated with pyrazo-lidinedione, isoxazolidinedione or barbituric acid ring systems were synthesized in order to obtain compounds of expected pharmacological value.

Experimental

All chemicals were obtained from Aldrich Chem. Comp., Wisconsin, USA and Fluka AG, Buchs, Switzerland.

Mp's are uncorrected and were determined in a Gallenkamp melting point apparatus. The TR spectra were obtained on Perkin-Elmer 580-B IR spectrophotometer.

4-bromomcthyl-6-methylcarbostyril(Ia) and the 7-chloro derivative (lb) were prepared according to the reported method (Chudgar and Trivet-di, 1969) 1-[(2-hydrox'-4- quinolyl)methyll malonic acid diethyl ester (IIa, b).

An alcoholic solution of sodium ethoxide (0.1 g Na in 30 ml abs. EtOH) was added to diethyl malonate (1.6g; 0.01mol) and stirred for 1 hr. Then the bromocthylcarbostyril derivative Ia or Ib (0.01 mol) was added and the reaction mixture was relluxed for a 3 hrs. The precipitate was filtered, washed with water and recrystallized from 5% CH_3OOOH.

Yields and physical data are as follows:

IIa: Yield: 315-317°C. Anal. Ca;cd. for $C_{18}H_{21}NO_5$C:65.24, H638, N:4.23. Found: C:65.13, H:6.33, N:4.18.
IIb: Yield: 67%, mp: 317-319°C. Anal. Caled. for $C_{17}H_{18}CINO_5$.C:58.04, H:5.15, N:3.98. Found: C:58.17, H:5.03, N:4.09.
2-4-x(2-Hydroxy-4-quinolyl)methyl]-3,5- pyrazolidinediones(IIIa, b).

A mixture of ester (0.002 mol) and 98% hydrazine hydrate (0 1g, 0.002 mol) in alcoholic sodium elhoxidc solution (0.02g in 10m1 abs. EtOH) was refluxed 7 hrs., filtered and the filtrate cooled then neutralized with 55'L. HO. The obtained precipitate was filtered off and recrystallized from 5% CH_3COOH to give IIIa and b.

Yield and physical data are as follows:
IIIa: Yield: 60%, mp:189-190°C. Anal Calcd. for $C_{14}H_{13}N_3O_3$. C: 61.98, 11:4.82, N:15.49. Found: 0:62.00, H: 4.95, N:15.53.
IIIb: Yield: 61%, mp:183°C. Anal Calcd for $C_{13}H_{10}CIN_3O_3$. C:53.52, H:3.45, N:14.4 Found: C:53.60, 11:3.3, N:14.31.
3-1-Phenyl-4[(2-Hydroxy-4-quinolyl)methyl]-3,5- pvrazolidinediones (IIIc and d).

The above procedure was applied but instead of hydrazine hydrate, phenyl-hydrazine was used. Compounds IIc-d were recrystallized from 5% CH_3COOH.

Yields and physical data are as follows:
IIIc: Yield: 70%, mp: 330-331°C, Anal. Calcd. for $C_{20}H_{17}N_3O_3$. C:69.15, H:4.93, N:12.09. Found: C:69.01, H:5.00, N:12.00.
IIId: Yield: 72%, nip: 313-314°C. Anal. Calcd. for $C_{19}M_{14}CIN_3O_3$. 0:6024, 11:3.83, N:11.41. Founded: C:60.12, H:4.00, N.115.0
4-4-[(2-Hydroxy-4-quinolyl)metbyl] isoxazolidine-3,5-diones (IVa, b)

A mixture of IIa or IIb (0.002 mol), NH_4OH(0.14g, 0.003 mol) and pyridine (5 ml) was heated under reflux for 4 hrs., cooled then poured into 5% HO to give IV and recrystallized from 5% CH_3COOH.
IVa: Yield: 50%, mp:282-283°C. Anal. Calcd. for $C_{14}H_{12}N_2O_4$. C:61,75, H:4,44, N:10.29. Found: 53,32, H:3.00, N:10.00.
IVb: Yield: 55%, mp: 256-258°C. Anal. Caled. for $C_{13}H_9CIN_2O_4$. C:53.34, H:3.09, N:9.56. Found: C:53.32, H:3.00, N:10.00.
5-5[(2-Hydroxy-4-quinaly0melhyl]harbituric acids (Va,b) and 5-[(2-Hydroxy-4-quinolyl) methyl] thiobarbitruic acids (Va, d).

A mixture of IIa of IIb(0.002 mol), urea (0.2g, 0.003 mol) or thiourea (0.2g, 0.0026 mol) in alcoholic sodium ethoxide solution (0.02g sodium in 10 ml abs. EtOH) was refluxed with stirring for 3 hrs., cooled, neutralized with cold 5% HCl and filtered. The precipitate was washed with water and recrystallized from 5% CH_3COOH.

Yield and physical data are as follows:
Va: Yield: 72%, mp: 305-307°C. Anal. Calcd. for $C_{15}H_{13}N_3O_4$.C: 60.19, H: 4,37,

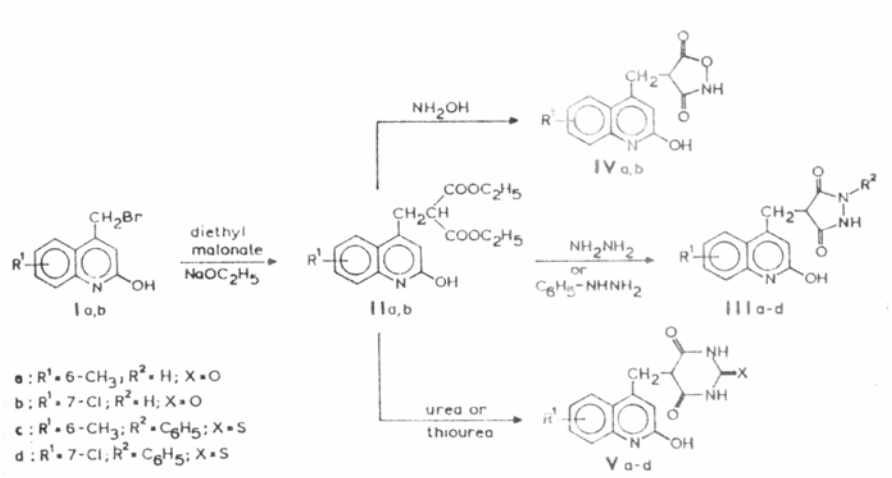
N: 14.04
Found: C60.27, H:4.23, N:13.93.
Vb: Yield: 75%, mp: 326-327°C. Anal. Calcd. For $C_{14}H_{10}$ CIN_3O_4. (C:52.50, H:3.12,
13. Found: C:52.63. H:3.16, N:13.6
Vc Yield: 60%, mp: 303-305°C. Anal. Calcd. for $C_{15}H_{13}N_3O_3S$.C:57.12, H:4.15, N:13.32. Found: C:56.97, H:3.98, NA 13.50.
Vd: Yield: 65%, mp: 314-315°C. Anal.Calcd. for $C_{14}H_{10}CIN_3O_3S$.C:50.07, H:3.00, N:12.50. Found: C:50.13, H: 3.09, N:12.43.

Results and Discussion

The key intermediates, [(2-hydroxy-4-quinolyl)methyll malonic acid diethyl esters IIa, b were prepared by the reaction of 4-bromomethylcarhostyrils la, b with ethyl sodium malonate.

Condensation of II with hydrazine hydrate in the presence of sodium ethoxide the 3,5-pyrazolidinediones III. In this way, both IIa and IIb were condensed with phenyl hydrazine giving the corresponding N-Phenyl-3,5-pyrazolidinediones IIIc and IIId. The isoxazolidine-3, 5- diones IVa, b were obtained by the reaction of II with hydroxylamine hydrochloride in the presence of pyridine.

Treatment of II with urea or thioura in the presence of sodium ethoxidc gave the barbituric or thiobarbituric acid derivatives Va-d (Scheme-1).



SCHEME 1

The ER spectra of all compounds are as expected and that of Vd showed bands attributable to NH(3335 cm^{-1}), C=0(1650 cm^{-1}). C = N(I590 cm^{1}),C= S(1280 cm^{-1} and N-C = S(1470 cm^{-1}).

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