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# SYNTHESIS OF PYRROLO[1,2-a] BENZO[f]INDOLE DERIVATIVES.

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Considerable attention has been given during the last decade to some metabolic products of a group of Streptomyces, "the mitomycines", which show remarkable antibiotic and antitumoral activity.

The structural feature, peculiar to these substances, is the 3H-pyrrolo[1,2-a] indole ring system (I).

It has been reported that even significant modifications of the structure of the mitomycines do not appear to alter considerably the basic biological activity (1,2,3).

We thought, therefore, it would be very interesting to prepare derivatives of the pyrrolo[1,2-a] benzo[f] indole which are obviously assimilated with the mitomycines.

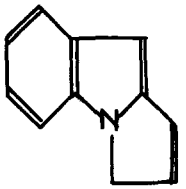
We have elaborated now an original method to synthetize the above mentioned compounds starting from derivatives of the dihydro-pyrrolizine.

Examining the resonance structures which can be written for a dihydropyrrolizine ring system, which is analogous to pyrrole, it is possible to infer that 5 car-

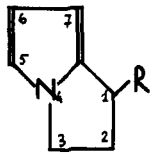
bon bears the highest electronic density as is confirmed by the formation of 5 substituted derivatives in formylation, acetylation and hydroxymethylation reactions (4-8).

It was therefore probable, that the activation of 5 position towards electrophilic substitution reactions such as Friedel-Crafts reaction with bicarboxylic acid anhydrides could yield carboxy-acyl-derivatives of type (III). These intermediates could easily be cyclized to the required quinones.

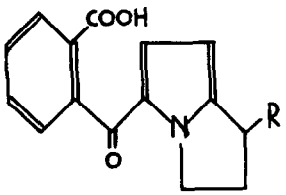
This hypothesis has been confirmed experimentally: in the present letter there is described, as an example, the synthesis of the quinone (IV) directly obtained by reaction between phthalic anhydride and 1-acetamido-1,2-dihydro-pyrrolizine (II) (9).



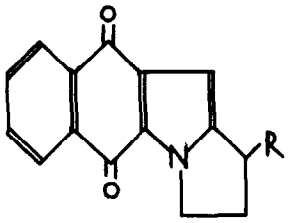
(I)




(II) R= -NH-CO-$CH_3$




(III) R= -NH-CO-$CH_3$




(IV) R= -NH-CO-$CH_3$

(V) R= $-NH_2$

(VI) R= -OH

1-acetamido-1,2,5,10-tetrahydro-3H-pyrrolo[1,2-a] benzo[f] indole-5,10-dione (IV).

A) 5.8 g (0.035 mole) of the amide (II) is mixed with 5.2 g (0.035 mole) of phthalic anhydride and 10.4 g (0.078 mole) of $AlCl_3$ in 50 ml of nitrobenzene; after 3 hours 9.8 g (0.073 mole) more of $AlCl_3$ and 40 ml of nitrobenzene is added and the heating is continued at 100-110°C for further 12 hours. The reaction mixture is worked out by acidification with HCl followed by alkalization and steam distillation of the nitrobenzene: chlorophorm extraction of the residuum yields 3.5 g of (IV); [yield 35%; yellow solid m.p. 320-1° dec. (chlorobenzene); U.V.: $\lambda_{max}^{EtOH}$ 210, 260, 330, 402 mμ ($\varepsilon$ =14500, 35900, 5800, 2600); I.R.: $\nu_{max}^{Nujol}$ 3300 (NH), 1660 (quinone C=O), 1640 $cm^{-1}$ (amide C=O)].

B) The acid (III) by heating at 70/80°C in nitrobenzene with $AlCl_3$ (mol. ratio 1/4.5) for 20 hours gives the quinone (IV), (yield 20%).

1-acetamido-5-(o-carboxy-benzoyl)-1,2-dihydro-pyrrolizine (III).

When the above described reaction is run by reacting the amide (II) with phthalic anhydride and $AlCl_3$ (molar ratio 1/2,2) for about 5 hours at 50/55°C it is possible to isolate the acid (III) [yield 25%; yellow-brown solid m.p. 135° dec. (benzene); U.V.: $\lambda_{max}^{EtOH}$ 210 and 302 mμ ($\varepsilon$ =19000 and 15700); I.R.: $\nu_{max}^{Nujol}$ 3300 (NH), 1710 (acid C=O) and 1620 $cm^{-1}$ (broad band: ketone C=O + amide C=O)]

1-amino-1,2,5,10-tetrahydro-3H-pyrrolo[1,2-a] benzo[f] indole-5,10-dione hydrochloride (V.HCl).

Acidic hydrolysis (HCl 4N) of the amide (IV) gives the amine (V) hydrochloride; [yield 90%; yellow-green solid m.p. 308°dec.; U.V.: $\lambda_{max}^{EtOH}$ 205, 277, 332, 374 s mμ ($\varepsilon$ =8800, 30000, 3800, 2000); I.R.: $\nu_{max}^{Nujol}$ 3400-2600 ($NH_3^+$), 1650 $cm^{-1}$ (quinone)].

By treatment of the hydrochloride with NaOH solution the free amine (V) is obtained; [yield 85%; orange-brown solid m.p. 200° (ethanol); U.V.: $\lambda_{max}^{EtOH}$ 206, 260, 330, 400 mμ ($\varepsilon$ =12700, 28300, 5100, 2600); I.R.: $\nu_{max}^{Nujol}$

3350 ($NH_2$), 1650 $cm^{-1}$ (quinone)].

1-hydroxy-1,2,5,10-tetrahydro-3H-pyrrolo[1,2-a] benzo[f] indole-5,10-dione (VI).

The deamination with $NaNO_2$ solution at 5/10° of the hydrochloride of the amine (V) gives the alcohol (VI); [yield 95%; yellow solid m.p. 202-206° (ethanol); U.V.: $\lambda_{max}^{EtOH}$ 210, 260, 332, 400 mμ (ε =10700, 30150, 4550, 2350); I.R.: $\nu_{max}^{Nujol}$ 3500 (-OH), 1650 $cm^{-1}$ (quinone)].

Further studies on this subject are underway and will be reported later.

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## REFERENCES

1) G.R. Allen Jr., J.F.Poletto and M.J.Weiss, J.Am.Chem.Soc.86,3877(1964).

2) G.R. Allen Jr., J.F.Poletto and M.J.Weiss, J.Org.Chem.30,2897(1965).

3) J.B.Patrick,R.P.Williams,W.E.Meyer,W.Fulmor,D.B.Cosulich, R.W.Broschard,J.S.Webb, J.Am.Chem.Soc.86,1889(1964).

4) A.A.Ponomarev,I.M.Skvortsov and A.A.Khorkin, Zh.Obshch.Khim.33(8), 2687-90(1963); C.A.60,489h(1964).

5) A.A.Ponomarev,I.M.Skvortsov and L.N.Astakhova, Dokl.Akad.Nauk SSSR 155(4), 861-4(1964); C.A.60,15813g(1964).

6) L.N.Astakhova,I.M.Skvortsov and A.A.Ponomarev, Zh.Obshch.Khim.34(7), 2410-12(1964); C.A.61,9455g(1964).

7) A.A.Ponomarev,L.N.Astakhova and V.I.Simontsev, Khim.Geterotsikl.Soedin., Akad.Nauk Latv.SSR,81-4(1965- 1); C.A.63,13189f(1965).

8) A.A.Ponomarev and L.N.Astakhova, Khim.Geterotsikl.Soedin.,Akad.Nauk Latv.SSR,221-5(1966- 2); C.A.65,2199h(1966).

9) Compound (II) has been prepared starting from the dihydro-pyrrolizine-1-one (10): this compound was easily converted to the corresponding oxime; this derivative by catalytic reduction (10% palladium on carbon) to the amine followed by acetylation yielded the required 1-acetamido-1,2-dihydro-pyrrolizine (II) [m.p. 124-5°C (benzene-light petroleum ether); U.V.: $\lambda_{max}^{EtOH}$ 220 and 295 mμ ($\varepsilon$ =8300 and 1400); I.R.: $\nu_{max}^{Nujol}$ 3220 (NH) and 1620 $cm^{-1}$ (amide C=O)].

10) G.R.Clemo and G.R.Ramage, J.Chem.Soc.,49(1931);
G.R.Clemo and T.A.Melrose, ibid.,424(1942);
V.Carelli,M.Cardellini and F.Morlacchi,Ann.Chim.(Rome),53,309(1963).