Possible Antifertility Compounds - Part IV: Syntheses of 2-(Phthalimido methylamino)-substituted benzanilides.

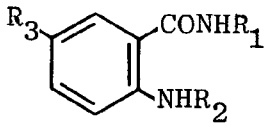
S. S. TIWARI, AMRAPALI UPRETI* AND R. K. SATSANGI,
Department of Chemistry, Lucknow University, Lucknow- India.

(Received 5th November, 1981)

Summary: Few benzanilides were synthesised by the condensation of N-Phthalimido-anthranilic acid chloride with several amines. The compounds tested did not show any post-coital effect for male fertility, and no antiimplantation activity was exhibited for female fertility.

Anthranilic acid has been found effective as an antiinflammatory[1], Analgesic[2] and C.N.S. depressant[3]. It is also a key intermediate in the biosynthesis of tryptophan, which is present in the N- terminal end of a decapeptide - leutinishing hormone relaeasing hormone (LH - RH). Mecklenberg et al[4] have demonstrated significant LH - RH activity in the N - terminal tripeptide (p- glutamic acid - histidine - tryptophan - NH_2) of LH - RH. Any change in N - terminal tryptophan could interfere with LH - RH activity. Substituted anthranilate could act as an antagonist in the biosyntheses of tryptophan and thus affect the release of leutinizing hormone.

Heindel et al[5] reported that the amido group of (I) at ortho position (R_1 = H) is the binding site of the molecule. In the anthranilamide synthesis during this work, the $CONH_2$ group has been substituted by aromatic amines. Such substitutions would further expose the $CONH_2$ group for binding. The analgesic activity of Hindel's compound was restrained when the amino group was substituted with an aromatic ring (R_2 = C_6H_5). In the present study, we substituted R_2 with phthalimodomethyl group, as the phthalic acid derivatives are known to inhibit spermatogenesis[6,7]. The synthetic route is given Fig. I.



I

Melting points were determined in open capillaries and are not corrected. The I.R. Spectrographs were recorded in KBr phase.

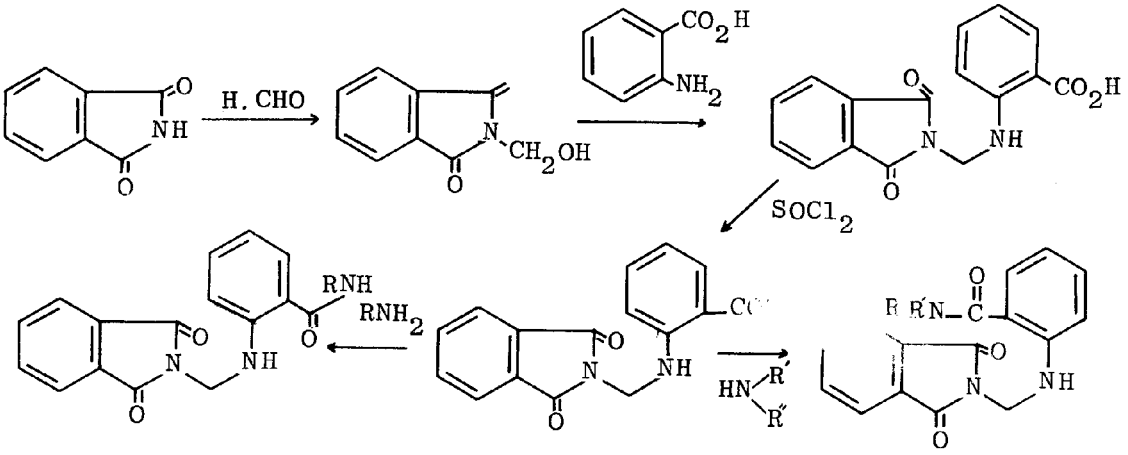
N - Hydroxmethyl phthalimide - Phthalimide (0.1M) was suspended in 100 ml. of water. To this suspension 37% formalin (0.12 M) was added. The reaction mixture was refluxed for an hour and was allowed to remain at room temperature overnight. The white residue, thus obtained, was subsequently filtered and dried in air. This was recrystallised from dilute ethanol. Yield 80%; m.p. = 138°; (lit[8] mp. = 138° - 141°). IR - 3550 cm^{-1}, 3050 cm^{-1}, 2900 cm^{-1}, 1710 cm^{-1}, 1300 cm^{-1} and 1050 cm^{-1} etc.

Phthalimido methyl anthranilic acid - Mannich tupe condensation was employed. N - Hydroxy - methyl - phthalimide (0.01 M) was dissolved in 25 ml. of ethanol by warming in a water bath. To this solution antharanlic acid (0.01 M) and two drops of Conc. HCl were added. The mixture, after stirring for half an hour at room temperature, was refluxed on a water bath for 3-4 hour. On cooling, a solid mass separated out. It was filtered and recrystallised from ethanol; m.p. 186°C (Lit.[9]- 188°C), I.R. 3330 cm^{-1}, 3050 cm^{-1}, 2900 cm^{-1}, 2650 cm^{-1}, 1710 cm^{-1}, 1690 cm^{-1}, 1650 cm^{-1}, etc.

Phthalimido methyl anthranilic acid chloride - A mixture of phthalimido methyl anthranilic acid (0.004 M) and thionyl chloride (00.0045 M) was suspended in dry chloroform and the reaction mixture was heated under reflux for 4-5 hour under anhydrous conditions. After cooling the mixture, chloroform was distilled off under reduced pressure and the curde acid chloride obtained was used for futher reaction without recrystallization.

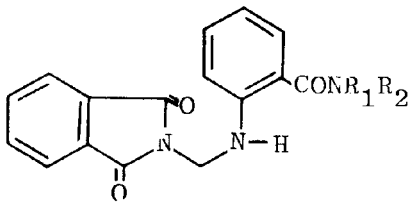
N-Phthalimido methyl anthranilamides - A mixture of Phthalimido methyl anthranilic acid chloride (0.002 M) and amines (primary or secondary) (0.002 M) and anhy. K_2CO_3 in 50 ml. of anhy. chloroform was

*Present address: C/o. Dr. G.C. Upreti, Chemistry Department, University of Delware, Newark, 19711, U.S.A.



Scheme I

Table 1



Compounds	NR_1R_2	M.P. °C	Mo. Formula*
1. p - anisidino.		65	$C_{23}H_{19}N_3O_4$
2. o - anisidino		95	$C_{23}H_{19}N_3O_4$
3. p - chloroanilino.		55	$C_{22}H_{16}N_3O_3Cl$
4. o - phenetidino		69	$C_{24}H_{21}N_3O_4$
5. p - phenetidino		94	$C_{24}H_{21}N_3O_4$
6. p - bromonilino		120	$C_{22}H_{23}N_3O_3$
7. Cyclohexylamino		62	$C_{23}H_{19}N_3O_3$
8. o - toluidino		70	$C_{23}H_{19}N_3O_3$
9. p - toluidino		81	$C_{22}H_{17}N_3O_3$
10. Anilino		95	$C_{22}H_{17}N_3O_3$
11. Morpholino		73	$C_{20}H_{19}N_3O_4$
12. Piperidino		87	$C_{21}H_{19}N_3O_3$
13. Diethylamino		102	$C_{20}H_{21}N_3O_3$

Elemental analysis for nitrogen corresponded will with the theory

refluxed on a water bath for 5-6 hours. After the reaction was complete, the solvent was removed by distillation under reduced pressure and the residue was treated with water and 5% sodium bicarbonate solution. A solid mass, which was obtained above, was recrystallized from a suitable solvent. Various compounds, thus prepared, are listed in table I. The IR spectrography of N-Phthalimido methyl anthranilic acid p-methoxy benzamide shows peaks at 3300 cm^{-1} 3250 cm^{-1}, 3050 cm^{-1}, 2900 cm^{-1}, 1710 cm^{-1}, 1670 cm^{-1}, 1659 cm^{-1}, and 1580 cm^{-1}, etc.

The absence of peak at 3550 cm^{-1}, 1300 cm^{-1}, and 1050 cm^{-1} and the presence of peaks at 3300 cm^{-1}, 2650 cm^{-1}, 1690 cm^{-1}, 1650 cm^{-1} in the prefinal compounds confirmed the utilization of OH group and the inclusion of NH and COOH group inthe prefinal compound. Similarly the absence of the peaks at 2650 cm^{-1} and 1690 cm^{-1} and the presence of peak at 1670 cm^{-1} in the I.R. spectrum of the final compounds confirmed the utilization of COOH group to form CONH group in the final compound.

Biological Activity

Anti - implantation screening - Three ccompounds, 2-(phthalimido methylamino)-4′ - chloro benzanilide, 2-(phthalimido - methyl amino) - 4′ - ethoxy benzanilide and 2-(phthalimidomethyl -2′ - methyl benzanilide were tested by the following method. Male rats are caged with the female at ratio of 1:4. Next day females showing the presence of spermatozoa in the vaginal smears were separated and divided in 4 groups each containing 5 rats. Group-1 served as control. Test compounds were given orally to others at 20 mg/kg/day for 7 days. The rats were killed at 7th day and laarotomised for recording the number of implantations in the uterus. The test compounds had no significant anti implantation activity at 20 mg/kg/day, as all the rats became pregnant.

2-(phthalimido methylamino) - 4′ ethoxy benzanilide was tested for postcoital activity in rats. Oral dose at 10 mg/kg/day of the drug, dissolved in propylene glycol was adminsitered for 4 days. The test compound did not show any postcoital activity and all animals tested got pregnant at the given dose.

Male antifertility screening - 2(phthalimidomethyl amino) -3,5-dibormo-5′-nitro benzalide was screened in male rats. The test compound dissolved in propylene glycol, was given orally at 100 mg/kg/day once daily for 5 days. The autopsy was performed on the third day after the last treatment. Seminal vesicle, prostate, and testes were weighed. No significant change in organ weight was found at 100 mg/kg/day. The effect on histology did not appear to be significant.

Acknowledgement

We thank Drs. Karten (Center for Population Research, National Institute of Health, U.S.A.) and Nityanand (C.D.R.I. Lucknow) for [illegible] screening of these compounds. Financial assistance was given by C.S.I.R., New Delhi, India.

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