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Studies in Antifertility Agents : Part XXVII — Synthesis of 2-Acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-*c*]quinolines†

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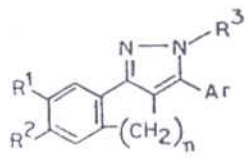
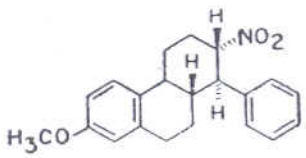
N-Tosyl-2,3-dihydro-4-quinolones (12-14), prepared from aniline, *m*- and *p*-anisidines by reported procedures, on condensation with araldehydes in the presence of NaOMe give the corresponding 3-arylidene-4-quinolones (15-18). Refluxing of 15-18 with NH_2-NH_2.H_2O in gl. AcOH affords the title compounds, 2-acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-*c*]quinolines (19-22). The stereochemistry of the title compounds based on the assignments of C_3-*H*, C_{3a}-*H*, C_4-H_2 protons has been studied by PMR decoupling experiments. In preliminary screening, compounds 19 and 22 have been found to prevent pregnancy at 20 mg/kg dose in female albino rats, but are ineffective at lower doses. None of the compounds tested shows any significant pharmacological activity.

THE contraceptive, abortifacient and antihypertensive activities exhibited by pyrazolobenzocycloalkanes (I)[1] and weak antifertility activity possessed by 1-phenyl-2-nitro-1,2,3,9,10,10a-hexahydrophenanthrene (II) (unpublished work) prompted us to investigate the antifertility activity of pyrazoloquinolines (III), in continuation[2] of our search for non-steroidal antiimplantation agents. In this paper, we report the synthesis and antifertility screening results of 2-acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a, 4, 5-tetrahydropyrazolo [4,3-*c*] quinolines (IV).



I



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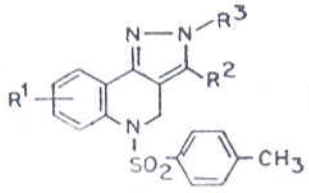


III

IV

The starting intermediates, N-tosyl-2,3-dihydro-4-quinolones **(12-14)** were prepared in a similar manner as described by Johnson *et al.*[3] and Speckamp *et al.*[4] except that ethyl acrylate, instead of methyl acrylate, was reacted with aromatic amines. Thus the addition of aniline or *m*-anisidine to ethyl acrylate in the presence of AcOH, or of *p*-anisidine in the presence of $SnCl_4$ gave ethyl β-anilinopropionates **(1-3)** as oil in good yields. Treatment of **1-3** with *p*-TsCl in pyridine yielded the corresponding N-tosyl propionates **(4-6)** as viscous oils which could not be purified by distillation and were, therefore, hydrolysed as such with methanolic KOH to give the corresponding N-tosyl acids **(7-9)**. In the case of acids **8-9**, the hydrolysis was accompanied by retero Michael reaction as is evident by the isolation of N-tosyl-*m*/*p*-anisidines **(10-11)** from the reaction mixture. The tosyl acids **(7-9)** were treated with PCl_5 to give acid chlorides which were cyclized under reported[3,4] Friedel-Crafts conditions in the presence of $AlCl_3$ or $SnCl_4$ to furnish the desired N-tosyl-2,3-dihydro-4-quinolones **(12-14)**. In the case of *m*-anisidino compound **(13)**, only 7-methoxyquinolone was formed.

Condensation of quinolones **(12-14)** with araldehydes in the presence of NaOMe in MeOH yielded crystalline N-tosyl 3-arylidene-4-quinolones **(15-18)** in good yields (Table 1). The PMR spectra‡ of these arylidenes **(15-18)** showed N—CH_2 protons as a doublet around 5.0 (J = 2 Hz) and arylideno olefinic proton as a triplet around 7.70 (J = 2Hz). The chemical shift of these arylideno protons[5] and their quantitative conversion[3] into dihydropyrazoles with $NH_2NH_2.H_2O$ suggested *trans*-configuration for arylidenes **(15-18)**. Refluxing of **15-18** with $NH_2NH_2.H_2O$ in gl. AcOH for 6-8 hr furnished the title compounds, 2-acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-*c*]-quinolines **(19-22)** in excellent yields (Table 1).

In the PMR spectra of **19-22**, C_3-*H*, C_{3a}-*H*, and C_4-H_2 exhibited interesting spectral features and the two protons of C_4-H_2 appeared at different chemical

†Communication No. 2632.

‡Chemical shift in δ (ppm) throughout the paper.

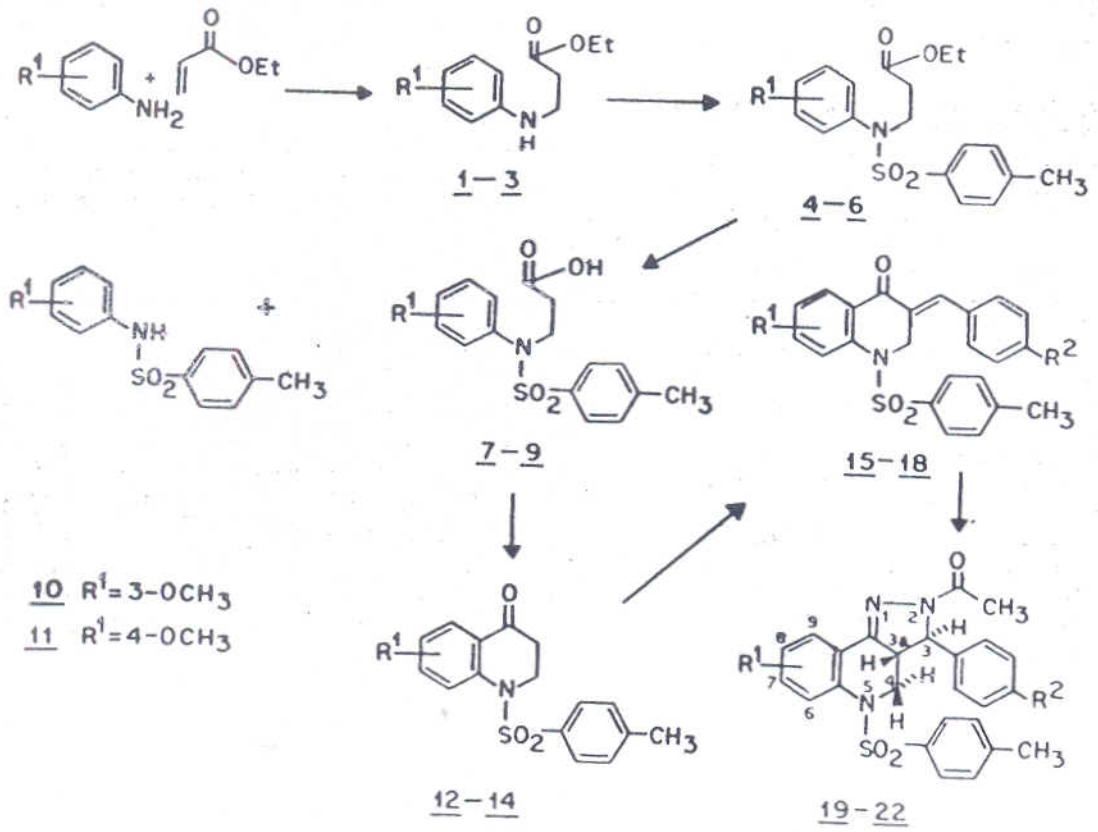
TABLE 1 — PHYSICAL AND SPECTRAL DATA OF N-TOSYL-3-ARYLIDENE-2,3-DIHYDRO-4-QUINOLONES (15-18) AND 2-ACETYL-3-ARYL-7/8-H(OR METHOXY)-3,3A,4,5-TETRAHYDROPYRAZOLO[4,3-c]QUINOLINES (19-20)

Compd*	R^1	R^2	m.p.† °C	Yield (%)	Mol. formula	Ana-lyzed for‡	NMR (CDCl$_3$)	ALD_{50}^{δ} mg/kg in mice
15	H	H	135	90	$C_{23}H_{19}NO_3S$	CHN	2.32 (*s*, 3, -C_6H_4-CH_3), 5.33 (*d*, 2, NCH_2, J=1.5Hz), 7.70 (*t*, 1, olefinic *H*, J= 1.5 Hz).	800
16	7-OCH_3	H	197	95	$C_{24}H_{21}NO_4S$	CHN	2.31 (*s*, 3, —C_6H_4—CH_3), 3.92 (*s*, 3, OCH_3), 5.17 (*d*, 2, NCH_2, J = 1.5 Hz), 7.92 (*d*, 1, C_5—*H*, J = 8Hz).	
17	7-OCH_3	OCH_3	148	94	$C_{25}H_{23}NO_4S$	CHN	2.30 (*s*, 3, —C_6H_4—CH_3), 3.82 (*s*, 3, OCH_3), 3.85 (*s*, 3, OCH_3), 4.98 (*d*, 2, NCH_2, J = 1.5 Hz), 7.78 (*d*, 1, C_5—*H*, J = 8.5 Hz).	
18	6-OCH_3	H	131	91	$C_{24}H_{21}NO_4S$	CNH	2.34 (*s*, 3, —C_6H_4—CH_3), 3.85 (*s*, 3, OCH_3), 5.02 (*d*, 2, NCH_2, J = 2Hz), 7.53 *t*, 1, olefinic *H*, J = 2Hz), 7.72 (d, 1, C_8-*H*, J = 9 Hz).	681
19	H	H	179	91	$C_{25}H_{23}N_3O_3S$	CHN	2.21 (*s*, 3, $COCH_3$), 2.24 (*s*, 3, —C_6H_4—CH_3), 2.30-2.70 (*m*, 1, C_{3a}-*H*), 3.48 (*t*, 1, C_4-*H*, J_g=J_v=14Hz), 4.48 (*dd*, 1, C_4-*H* J_g = 14 Hz, J_v=5 Hz), 4.70 (*d*, 1, C_3-*H*, J = 10 Hz).	800
20	7-OCH_3	H	216-17	53	$C_{26}H_{26}N_2O_4S$	CHN	2.23 (*s*, 6, $COCH_3$ and —$C_6H_4CH_3$), 2.34 (*m*, 1 C_{3a}-*H*, enveloped in the signal of $COCH_3$ and —$C_6H_4CH_3$), 3.47 (*t*, 1, C_4-*H*, J_g = J_v = 14 Hz), 3.79 (*s*, 3, OCH_3), 4.47 (*dd*, 1, C_4-*H*, J_g = 13 Hz, J_v = 5Hz), 4.69 (*d*, 1, C_3-*H*, J = 10 Hz), 7.70 (*d*, 1, C_9-*H*, J = 9 Hz).	
21	7-OCH_3	OCH_3	224	70	$C_{27}H_{27}N_2O_5S$	CHN	2.19 (*s*, 3, $COCH_3$), 2.23 (*s*, 3,—$C_6H_4CH_3$), 2.42 (*m*, 1, C_{3a}-*H*. enveloped in the signal of $COCH_3$ and —$C_6H_4CH_3$), 3.43 (*t*, 1, C_4-*H*, J_g = J_v = 13 Hz), 3.73 (*s*, 3, OCH_3), 3.78 (*s*, 3, OCH_3), 4.48 (*dd*, 1, C_4-*H*, J_g = 13 Hz, J_v = 5Hz), 4.62 (*d*, 1, C_3-*H*, J = 10 Hz), 7.70(*d*, 1, C_9-*H*, J = 8 Hz).	
22	8-OCH_3	H	198	97	$C_{24}H_{24}N_2O_4S$	CHN	2.21 (*s*, 3, $COCH_3$), 2.24 (*s*, 3, —$C_6H_4CH_3$), 2.40 (*m*, 1, C_{3a}-*H*), 3.48 (*t*, 1, C_4-*H*, J_g = J_v = 14 Hz), 3.78 (*s*, 3, OCH_3), 4.42 (*dd*, 1, C_4-*H*, J_g = 14 Hz, J_v = 5 Hz), 4.67 (*d*, 1, C_3-*H*, J = 10 Hz), 7.71 (*d*, 1, C_6H, J = 9 Hz).	681

*Compounds **2**, **3**, **5**, **6**, **8** and **9** were prepared by the reported procedures[3,4] for their methyl analogs. Compounds **16-18** and **20-22** were prepared by the method described in experimental section for **15** and **20** respectively. †All compounds were recrystallized from MeOH. ‡All compounds were analyzed within ± 0.5%. δCompounds **16**, **17**, **20** and **21** are under testing for their pharmacological activity.

shifts. The assignment of these protons and their stereo-orientation was determined by decoupling experiments in the case of compounds **19** and **22**. In **19**, C_3-*H* appeared as a doublet at 4.70 (J= 10 Hz) which corresponds to C_3, C_{3a} *trans*-configuration in such systems[6]. The multiplet of C_{3a}-*H* enveloped in the signals of $COCH_3$ and CH_3 was located by decoupling at 4.70 which affected the multiplicity of the signals at 2.30-2.70. By decoupling experiments, the two protons of C_4—H_2, adjacent to asymmetric carbon C_{3a}, were assigned. One of the C_4—*H* appeared as a triplet at 3.48 (J=14 Hz) due to geminal (J_g=14 Hz) and vicinal (J_v=14 Hz) couplings. Such a vicinal coupling constant (14 Hz) is indicative of *trans*- telationship to C_{3a}-*H*. The other C_4—*H* appeared as double doublet at 4.48 (J_g=14 Hz and J_v=5 Hz) which is suggestive of its *cis*-orientation with respect to C_{3a}—*H*. Similar decoupling experiments in the PMR spectrum of **22** proved to be useful in assigning C_4H_2 and its stereochemistry. In analogy to the PMR spectra of **19** and **22**, it is presumed that **20** and **21** would have similar spectral features on decoupling. The PMR spectral data of all these compounds are given in Table 1 and the stereochemical structure of **19-22** is depicted in Scheme 1.

The preliminary antiimplantation and pharmacological screening of these compounds were carried out by the reported procedures[5,7]. Compounds **19** and **22** inhibited pregnancy at 20 mg/kg dose in female albino rats and were ineffective at lower doses. No improvement in this activity could be achieved by



SCHEME 1

structural modification of **19**. Interestingly 7/8-unsubstituted or 8-methoxy compound showed activity while the corresponding 7-methoxy analog was inactive which indicated that unsubstituted 7-position is preferred for this activity. Substitution in 3-phenyl group destroyed the activity. Earlier, we have reported[2] that the corresponding B-ring seco compounds lacking N-tosyl group were ineffective as antifertility agents. Thus, the skeleton present in **19** appears to be a likely framework for the antifertility activity of such a system.

No significant pharmacological activity was exhibited by the compounds tested.

Experimental Procedure

M.ps and b.ps are uncorrected. Purity of the compounds was routinely checked on silica gel-G TLC plates using C_6H_6 or C_6H_6—MeOH as mobile phase. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer infracord 137, 157 or 177 model. PMR spectra were recorded in $CDCl_3$ on a Varian A-60D or a Perkin Elmer R-32 spectrometer using TMS as internal standard.

Ethyl β-anilinopropionate (**1**) — A mixture of aniline (139.5 g, 1.5 mol), ethyl acrylate (165 g, 1.65 mol) and AcOH (5 ml) was refluxed for 15 hr and the reaction mixture distilled *under vacuo* to give **1**, yield 210 g (71%), b.p. 127-30°/0.4 mm Hg, n_D^{33} = 1.5220, PMR : 1.23 (*t*, 3, C—CH_3, *J*=7Hz) 2.58 (*t*, 2, C—CH_2, *J*=7Hz), 3.43 (*t*, 2, N—CH_2, *J*= 7 Hz), 3.85 (*s*, 1, N*H*, D_2O exchangeable), 4.14 (*q*, 2, OCH_2, *J* = 7Hz) (Found : C, 68.00; H, 8.27; N, 7.75. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%).

Ethyl N-tosyl-β-anilinopropionate (**4**) — To a cooled and stirred solution of **1** (96.5 g, 0.5 mol) in pyridine (1 litre), *p*-TsCl (114.5 g, 0.6 mol) was added in small lots. After stirring for 15 min at this temperature, the reaction mixture was heated on a steam-bath for 30 min and then just to refluxing. The reaction mixture was poured onto ice-HCl and extracted with ether. The extract was washed successively with 3*N* HCl, water, 1% KOH, water and saturated NaCl solution, dried (Na_2SO_4) and solvent removed to give **4**, yield 168 g (97%); PMR: 1.18 (*t*, 3, C—CH_3, J=7 Hz), 2.41 (*s*, 3, —C_6H_4—CH_3), 2.55 (*t*, 2, C—CH_2, *J*=8. Hz), 3.88 (*t*, 2, N—CH_2, *J*=8 Hz), 4.05 (*q*, 2, OCH_2, *J*=7 Hz), (Found : C, 59.90; H, 5.95; N, 3.64. $C_{18}H_{21}NO_4S$ requires C, 60.25; H, 6.05; N, 4.03%).

N-Tosyl-β-anillinopropionic acid (**7**) — To a stirred solution of ester **4** (168 g, 0.48 mol) in 80% aq. MeOH (1400 ml), 10% KOH (380 ml) was added at room temperature during 30 min. The reaction mixture was stirred at room temperature for 4 hr and allowed to stand overnight. The clear solution was diluted with water (2 lit) and poured with stirring into cold dil. HCl. The separated acid was filtered, washed with cold water, dried and recrys-

tallized from C_6H_6 to get **7**, yield 143 g (92%), m.p. 145°.

N-Tosyl-2,3-dihydro-4-quinolones (**12-14**) — Cyclization of acids **7-9** with PCl_5-$AlCl_3$ or $SnCl_4$ by the reported procedure[3,4] gave **12-14** in 86, 63 and 70% yields respectively.

N-Tosyl-3-benzylidene-2,3-dihydro-4-quinolone (**15**) —A solution of benzaldehyde (3.18 g, 30 mmol) in MeOH (6 ml) was added to a cold (15°) solution of sodium (0.3 g, 13 mmol) in MeOH (30 ml). To this stirred solution, **12** (9.03 g, 30 mmol) was added at 15°. The reaction mixture was allowed to attain room temperature and continuously stirred for 4 hr. The product separated was filtered and washed with methanol to get **15**, yield 10.95 g (94%), m. p. 135°.

Similarly **16-18** were prepared in yields given in Table 1.

2-Acetyl-3-phenyl-5-tosyl-3, 3a, 4, 5-tetrahydropyrazolo[4,3-c]quinoline (**19**) — A mixture of benzylidene **15** (5.46 g, 14 mmol), NH_2—$NH_2.H_2O$ (5.6 ml, excess) and gl. AcOH (50 ml) was refluxed for 6-8 hr. The reaction mixture was cooled, poured onto ice, and the precipitated product was filtered, washed with water and crystallized from MeOH to get **19**, yield 5.7 g (91%), m.p. 179°.

Similarly **20-22** were obtained in yields given in Table 1.

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