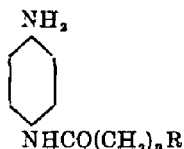


SYNTHESIS OF NEW LOCAL ANAESTHETICS. PART VII

BY K. N. GAIND AND P. N. VOHRA

Some diethylamino and piperidino derivatives of acetyl—and propionylaminoanilines have been prepared and their local anaesthetic properties studied.

It has been established by Gaind, Ray and co-workers (*J. Indian Chem. Soc.*, 1940 17, 400, 619) that a simple amido group in a compound can act as an anchor for the production of local anaesthetic properties. It has been shown (*loc. cit.*) that quinolines having the side-chain in position 8 were found to have pronounced local anaesthetic properties yet its value as a therapeutic is very doubtful as the quinolines are well known irritants. In the present work the quinoline group has been replaced by an aniline group, thus synthesising substances with non-irritating properties of the general formula



where $n=1$ or 2 and $\text{R}=\text{N}\cdot\text{Et}_2$ or piperidyl. The NH_2 may be in *ortho*, *meta*, or *para* position.

The dihydrochloride of *o*-amino- β -diethylaminopropionanilide, and *p*-amino- β -piperidinopropionanilide have been found to have as strong anaesthetic properties as cocaine hydrochloride, when tested by Rabbit's cornea method.

EXPERIMENTAL

Preparation of p-Nitrochloroacetanilide.—*p*-Nitroaniline (2 g.) was suspended in dry benzene (30 c.c.) and a solution of chloroacetyl chloride (1.4 c.c.) in dry benzene (20 c.c.) was added to it gradually during 15 minutes at 15° . It was refluxed on a water bath for 2 hours and then cooled. The yellow precipitate was washed several times with water, dried and crystallised from alcohol as yellow plates, m.p. 191° . (Found : N, 13.11 ; Cl, 16.55. $\text{C}_8\text{H}_7\text{O}_2\text{N}_2\text{Cl}$ requires N, 13.08 ; Cl, 16.53 per cent).

p-Nitropiperidinoacetanilide.—The solution of the above chloro compound (2 g. in absolute alcohol (30 c.c.) with piperidene (2 c.c.) was refluxed on a water-bath for 4 hours. On cooling, needles separated out which after being washed several times with water recrystallised from absolute alcohol as rectangular plates, m. p. $143\text{--}44^\circ$ (Found : N, 15.76. $\text{C}_{13}\text{H}_{17}\text{O}_2\text{N}_3$ requires N, 15.97 per cent).

p-Aminopiperidinoacetanilide.—Piperidinoacetyl-*p*-nitroaniline (2 g.) was dissolved in acetic acid (30 c.c., 50%) and zinc dust (14 g.) was added to it in small quantities at a time. The temperature at once rose to 40° and was maintained as such throughout the addition of zinc dust. Afterwards it was heated on a water-bath at 60° for 3 hours and filtered. The filtrate was cooled in ice and ammonium chloride (20 g.) was added

o it. The reaction mixture was made alkaline with ammonia and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and ether recovered. The residue thus obtained was dissolved in dry ether and treated with ethereal hydrogen chloride till acidic. On cooling in ice for 2 hours a white product separated out which was washed with dry ether repeatedly and then crystallised from alcohol-ether mixture, n.p. 258-59° (decomp.). (Found : N, 13.4 ; Cl, 22.98. $C_{11}H_{21}ON_2Cl_2$ requires N, 13.6 ; Cl, 23.2 per cent).

p-Nitrodiethylaminoacetanilide.—It was prepared using the corresponding chloro compound (3 g.) in absolute alcohol (50 c.c.) and adding diethylamine (4.3 c.c.) in an analogous way and was crystallised from low boiling petroleum ether as long needles, m.p. 59-70°. (Found : N, 16.35. $C_{12}H_{17}O_2N_3$ requires N, 16.66 per cent).

TABLE I

Name of substance	Crystallised from	M.p.	Analysis	
			Found,	Calc.
<i>o</i> -Nitrochloroacetanilide	Dil. alcohol	94°	N, 13.4% Cl, 16.3	N, 13.08% Cl, 16.37
<i>o</i> -Nitrodiethylaminoacetanilide	"	72°	N, 16.45	N, 16.7
<i>o</i> -Aminodiethylaminoacetanilide dipicrate	Alcohol-ether	193° (decomp.)	N, 18.58	N, 18.56
<i>o</i> -Aminopiperidinoacetanilide dipicrate	Acetone-ether	245° (decomp.)	N, 18.37	N, 18.29
<i>o</i> -Nitro- β -chloropropionanilide	Dil. alcohol	90°	N, 12.4 Cl, 15.1	N, 12.3 Cl, 15.53
<i>o</i> -Nitro- β -diethylamino-propionanilide picrate	Alcohol-benzene	162-63°	N, 17.36	N, 17.1
<i>o</i> -Amino- β -diethylamino-propionanilide dipicrate	Alcohol-benzene	180°	N, 18.62	N, 18.2
<i>o</i> -Nitro- β -piperidinopropionanilide dipicrate	"	174°	N, 16.21	N, 16.5
<i>o</i> -Amino- β -piperidinopropionanilide dipicrate	"	170°	N, 18.72	N, 18.2
<i>m</i> -Nitrochloroacetanilide	"	174°	N, 13.3 Cl, 16.4	N, 13.08 Cl, 16.37
<i>m</i> -Nitropiperidinoacetanilide	Dil. alcohol	95°	N, 15.5	N, 15.97
<i>m</i> -Aminopiperidinoacetanilide dipicrate	"	200°	N, 18.5	N, 18.29
<i>m</i> -Nitrodiethylaminoacetanilide	Benzene	47°	N, 16.5	N, 16.7
<i>m</i> -Aminodiethylaminoacetanilide dipicrate	"	109°	N, 18.53	N, 18.56
<i>m</i> -Nitro- β -chloropropionanilide	Alcohol	97°	N, 12.1 Cl, 15.2	N, 12.3 Cl, 15.53
<i>m</i> -Nitro- β -diethylamino-propionanilide	Dil. alcohol	88-90°	N, 15.7	N, 15.9
<i>m</i> -Amino- β -diethylamino-propionanilide dipicrate	Alcohol-ether	220-21° (decomp.)	N, 18.5	N, 18.2
<i>m</i> -Nitro- β -piperidino-propionanilide	Dil. alcohol	199°	N, 15.3	N, 15.16
<i>m</i> -Amino- β -piperidinopropionanilide dipicrate	Alcohol-benzene	110°	N, 18.4	N, 18.2

p-Aminodiethylaminoacetanilide dihydrochloride was also prepared in a manner analogous to the corresponding piperidine compound. It was crystallised from alcohol ether mixture, m.p. 237-38° (decomp.). (Found : N, 14.0 ; Cl, 23.9. $C_{12}H_{21}ON_2Cl$ requires N, 14.3 ; Cl, 24.1 per cent).

p-Nitro- β -chloropropionanilide was prepared using *p*-nitroaniline (5 g.) in dry benzene (60 c.c.) and a solution of β -chloropropionyl chloride (3 c.c.) in dry benzene (10 c.c.) in a manner already described for chloroacetyl compound. It was crystallised from alcohol in yellow needles, m.p. 171°. (Found : N, 13.2 ; Cl, 15.79. $C_9H_{13}O_2N_2Cl$ requires N, 12.8 ; Cl, 15.52 per cent).

p-Nitro- β -diethylaminopropionanilide was prepared from the foregoing chloro compound in the usual way. It was crystallised from low boiling petroleum ether as long white needles, m.p. 96°. (Found : N, 15.5. $C_9H_{19}O_2N_2$ requires N, 15.9 per cent).

p-Amino- β -diethylaminopropionanilide dihydrochloride was prepared in a similar way as described for the corresponding acetyl compound, and crystallised from alcohol ether mixture, m.p. 335° (decomp.). (Found : N, 13.9 ; Cl, 23.2. $C_{13}H_{23}ON_2Cl_2$ requires N, 13.8 ; Cl ; 23.05 per cent).

TABLE II

(The figures in the parenthesis are for cocaine which is used as standard)

Substance	Time for onset of anaesthesia ; complete loss of reflex action	Duration for which complete loss of reflex action lasted
<i>p</i> -Aminodiethylaminoacetanilide dihydrochloride	Never complete (1 minute)	Incomplete anaesthesia lasted for 4 minutes (37 minutes)
<i>p</i> -Aminopiperidinoacetanilide dihydrochloride	Never complete (1 minute)	Incomplete anaesthesia lasted for 25 minutes (36 minutes)
<i>p</i> -Amino- β -diethylaminopropionanilide dihydrochloride	Never complete (1 minute)	Incomplete anaesthesia lasted for 15 minutes (36 minutes)
<i>p</i> -Amino- β -piperidinopropionanilide dihydrochloride	4 minutes (1½ minute)	36 minutes (37 minutes)
<i>o</i> -Aminodiethylaminoacetanilide dihydrochloride	5 minutes (1½ minute)	30 minutes (35 minutes)
<i>o</i> -Aminopiperidinoacetanilide dihydrochloride	6 minutes (1 minute)	20 minutes (36 minutes)
<i>o</i> -Amino- β -diethylaminopropionanilide dihydrochloride	2 minutes (1 minute)	36 minutes (36 minutes)
<i>o</i> -Amino- β -piperidinopropionanilide dihydrochloride	Never complete (1½ minute)	Incomplete anaesthesia lasted for 20 minutes (37 minutes)
<i>m</i> -Aminodiethylaminoacetanilide dihydrochloride	Never complete (1 minute)	Incomplete anaesthesia lasted for 20 minutes (37 minutes)
<i>m</i> -Aminopiperidinoacetanilide dihydrochloride	Never complete (1½ minute)	Incomplete anaesthesia lasted for 15 minutes (36 minutes)
<i>m</i> -Amino- β -diethylaminopropionanilide dihydrochloride	5 minutes (1 minute)	20 minutes (37 minutes)
<i>m</i> -Amino- β -piperidino-propionanilide dihydrochloride	Never complete (1 minute)	Incomplete anaesthesia lasted for 30 minutes (36 minutes)

p-Nitro- β -piperidinopropionanilide was prepared from the corresponding chloro compound, in an analogous way as described for diethylamino compound using piperidine in place of diethylamine. It was crystallised from 50% alcohol, m.p. 100° (decomp.). Found : N, 14.96. $C_{14}H_{15}O_3N_3$ requires N, 15.16 per cent).

p-Amino- β -piperidinopropionanilide was prepared in a similar way by the reduction of the above nitro compound as rectangular plate, m.p. 96°. (Found : N, 17.2. $C_{14}H_{21}O_2N_2$ requires N, 17.05 per cent.)

The dihydrochloride was crystallised from alcohol-ether mixture, m.p. 335° (decomp.). Found : N, 13.12; Cl, 21.6. $C_{14}H_{23}ON_3Cl_2$ requires N, 13.16; Cl, 21.7 per cent).

The compounds prepared from *o*- and *m*-nitroanilines are shown in Table I.

The above substances were tested for local anaesthetic activity by rabbit's cornea method and Table II shows the results.

From the foregoing table it appears that dihydrochlorides of *o*-amino- β -diethylaminopropionanilide, and *p*-amino- β -piperidinopropionanilide have as strong anaesthetic properties as cocaine hydrochloride. The time for onset of anaesthesia, however, is longer in these cases than with cocain hydrochloride.

The authors are very thankful to Dr. J. N. Ray, Director, Drugs and Dressing, Department of Supply, New Delhi, for his keen interest in this work.

UNIVERSITY INSTITUTE OF CHEMISTRY,
LAHORE.

Received July 9, 1945.