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Contents

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Synthetic Outlines of Industrially used local anaesthetics - A review

Dr P K Ghosh*

Summary

In this paper, the synthetic outlines of the significantly used local anaesthetic chemicals in the different parts of the world has been summarised. In this limited context, only 34 compounds could be identified; 18 of these were esters of general formula I, 8 were amides of general formula II and 8 others were compounds having functional groups of carbonic acid esters, imides, ethers and ketones. The main properties and uses of these compounds along with the important companies marketing them (with their brand names) are also described in three tables. Compounds of formula I and II are represented by 2-Z, 3-Y, 4-X, C_4H_3. $CO.O.CH(R_1)$. $C(R_2)(R_3)(R_4)$ AND $2\text{-}X_1$, $6Y_1$ C_4H_4. NH. CO. R respectively where X,Y,Z, R_1, R_2, R_3, R_4, X_1, Y_1 and R are various substituents.

Introduction: The class of chemicals which produce a condition of insensibility, that is loss of feeling, in man and animals in a small area surrounding the site of application of the chemicals, belong to the group of "Local Anaesthetics". Local anaesthesia is produced at the selected site by such chemicals by temporarily desensitising the sensory nerves or their endings. Local anaesthetics act on the nervous system including every type of the nerve fibres. The condition of local anaesthesia produced is reversible and the nerve fibre or the nervous system comes to the normal state without any damage after the action of the local anaesthesia is over. Local anaesthetics are used in surgery specially in situations where general anaesthesia is risky or inconvenient. These are extensively used in minor surgery, gynaecology and dentistry. They are also used for relieving pain of skin and mucous membranes. Such chemicals are many in numbers and the literature on the subject is vast (1 to 6). However, the large number of identified chemicals found to have local anaesthetic properties, a relat-

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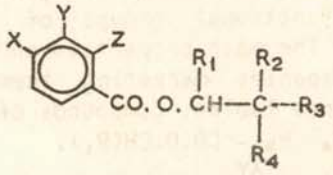
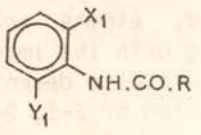
ively small numbers, of the order of thrity four have really stood the pharmacological, clinical and other requirements for their use in finished pharmaceutical formulations for applications in men and animals. The main reason for this has been the relatively narrow safety margins of most of these chemicals.

The theme of this paper has been to outline the synthetic facets of the compounds which were or are in commercial use significantly in one part of the world or the other as a local anaesthetic drug. In this limited context only thirty four compounds could be identified upto the time of preparing this paper. Such identified compounds were found to have varying functional moities like esters, amides, ethers, ketones etc. A majority of these could be depicted by the general formula I, in which an aromatic acid was attached to an aliphatic side chain by an ester linkage, or the general formula II where an aromatic amine was connected to an aliphatic carboxylic acid moietly through an amide bond. These are shown below:



FORMULA-I(ESTERS)



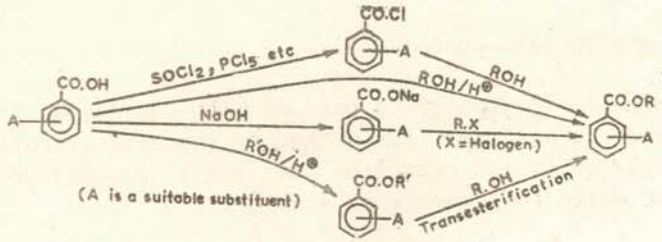
FORMULA-II(AMIDES)

When $X, Y, Z, R_1, R_1, R_4, R_4, X_1, Y_1$, and R represent various substituents as discussed in the text and Tables I and II. Eighteen compounds of Formula I (Table I) and eight or Formula II (Table II) have been used commercially to a great extent as discussed in the following text. Eight other chemicals ((Table III) also used commercially quite extensively as discussed subsequently, could not be depicted by any general skeletal structure, although there existed appreciable structural similarity among some of them. The Tables (I, II and III) enlist the generic/common names, molecular formulae and molecular weights of these compounds and important brand names with main companies who introduced them.

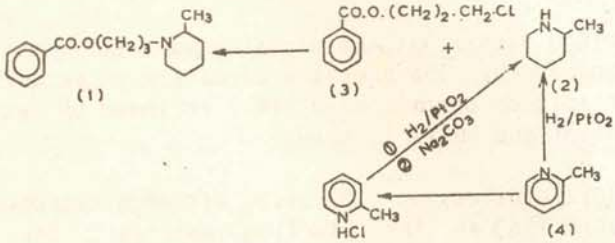
2.Synthetic Facets:

A. The compounds represented by FORMULA-I (Esters):

These compounds are synthesised by using benzoic acid or substituted benzoic acid as one moiety and an appropriate alkanol as the other moiety as schematically shown below:

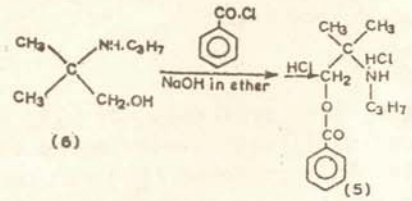


The synthesis (7) of PIPEROCAINE (1) starts with 2-methylpiperidine (2), which is condensed with 3-chloropropyl benzoate (3). The starting material (2) is conveniently obtained by the catalytic hydrogenation of alpha picoline (4) abundantly available; the catalytic hydrogenation has been found to be better than the sodium alcohol reduction method used earlier (6).

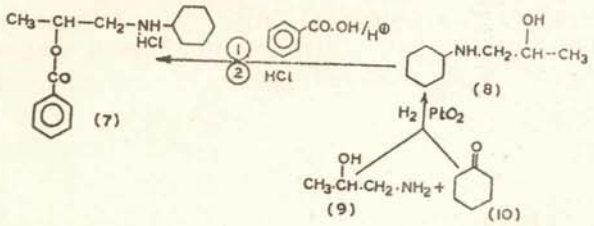


Compound (3) could be easily obtained by the condensation of 1-bromo 3-chloropropane with benzoic acid in the presence of soda ash.

MEPRYLCAINE (5) is synthesised (9) from the aminoalcohol (6) which is benzoylated in the cold etherial medium in the presence of acqueous sodium hydroxide, followed by treating the resulting oil with concentrated hydrochloric acid which leads to the formation of (5) as the hydrochloride through N to O acyl migration (10).



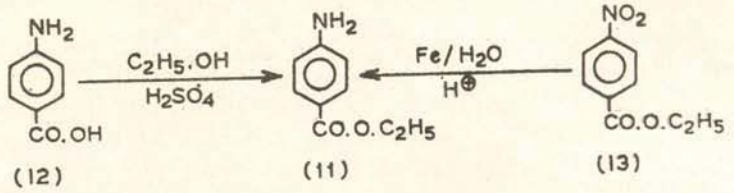
HYXYLACAINE (7) as the hydrochloride is obtained (11) by the benzaylation of the intermediate (8), followed by hydrochlorination. The intermediate compound (8) is obtaineed in almost quantitative yield from isopropyl amine 9 and cyclohexanone (10) by reductive amination in presence of Platinum dioxide.



The compound (9) could be conveniently perepared by reacting propylene oxide

with ammonia under appropriate conditions.

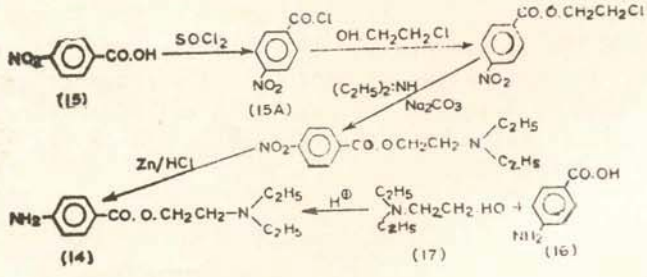
ETHYLAMINOBENZOATE (11), which is one of the earliest known local anaesthetic compound, is prepared (12) either by the esterification of para aminobenzoic acid (12) or by the reduction of ethyl paranitrobenzoate (13) with iron powder and water in presence of a acid (13).



(12) (11) (13)

The commercial method uses (13) as the starting material, which in turn is conveniently produced by the pressure oxidation of paranitro toluene with commercial nitric acid or chromic acid (14), followed by esterification of the acid with ethanol and sulfuric acid.

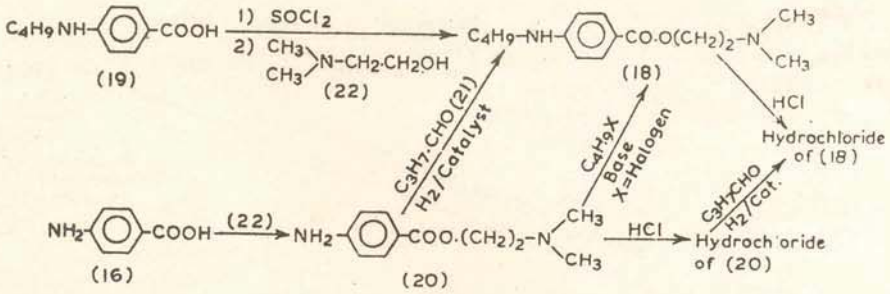
PROCAINE (14) is synthesised (15) using either p-nitrobenzoic acid (15) of p-aminobenzoic acid (16) as the starting material. The reductant zinc-hydrochloric acid shown below for the conversion of nitro group can be replaced by the cheaper Fe/HCl reduction method.



(15) (15A) (14) (17) (16)

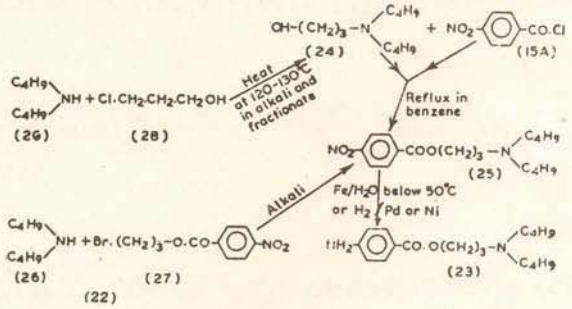
A novel method for the synthesis of (14) used industrially, utilises trans-esterification of (11) with diethylamino ethanol (17) using sodium ethoxide as the catalyst. The compound (17) is conveniently synthesised from ethylene oxide (16) or ethylene chlorohydrin (17) and diethylamine.

TETRACAINE (18) is prepared (18) by coverting 4-n-butylaminobezoic acid (19) into its dimethylaminoethyl ester by the usual procedure or by butylating dimethylaminoethyl p-aminobenzoate (20), obtained from p-aminobenzoic acid (16). Reductive Schiff's condensation (19) of (20) with n-butyraldehyde (21), or the reaction product of the hydrochloride of (20) with n-butyraldehyde (21), followed by hydrogenation also produces (18) or its hydrochloride as schematically represented below:

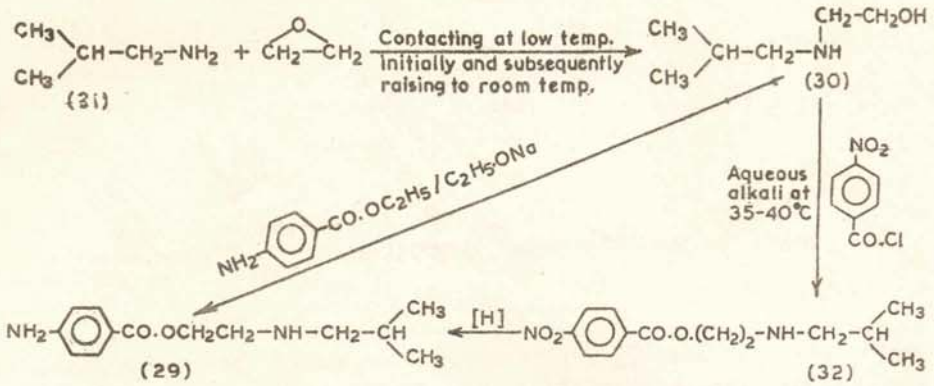


Dimethylamino ethanol (22), the key synthon could be conveniently prepared like (17) by the condensation of dimethylamine with ethylene oxide under appropriate conditions and the product could be isolated by fractionation under vacuum.

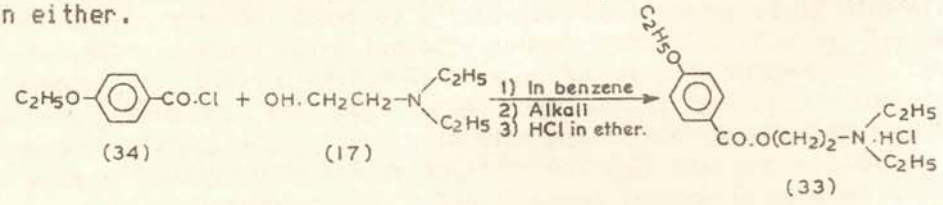
BUTACAINE (23) is synthesised (20) by the condensation of p-nitrobenzoyl chloride (15 A) with 3-di-n-butylamino propanol (24) in benzene under reflux conditions, followed by iron powder - water reduction or catalytic hydrogenation of the resulting nitroalcohol ester (25). The compound (25) may be prepared alternatively by alkylating (21) di-n-butyl amine (26) with 3-bromopropyl paranitro benzoate (27) The starting aminoalcohol (24) is prepared by condensation between di-n-butyl amine (26) and 3-chloropropan 1-ol (28)



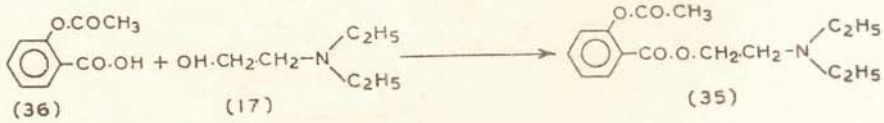
In the synthesis (22) of BUTETHAMINE (29) the preparation of the isobutylamino ethanol (30) plays a major role. Treatment of isobutylamine (31) in aqueous medium with ethylene oxide gives the aminoalcohol (30) in high yield (23). Condensation of the latter with p-nitrobenzoyl chloride in aqueous alkaline solution and subsequently reducing the resulting ester (32) with tin and hydrochloric acid gives (29); the reduction could also be accomplished by the use of cheaper iron and hydrochloric acid. The synthesis could also be accomplished by trans-esterification of (30) with ethylparaamino benzonate (11) under low pressure using sodium ethylate as catalyst.



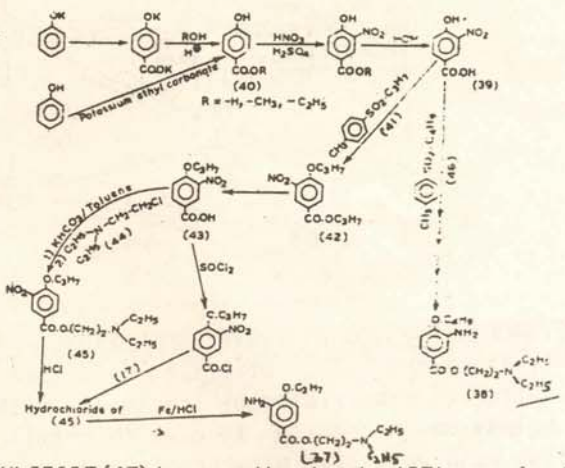
PARETHOXYCAINE (33) as its hydrochloride is produced (24) by the condensation between p-ethoxybenzoyl chloride (34) and 2-diethylamino ethanol (17), basifying the reaction product and treating the base with hydrogen chloride in either.



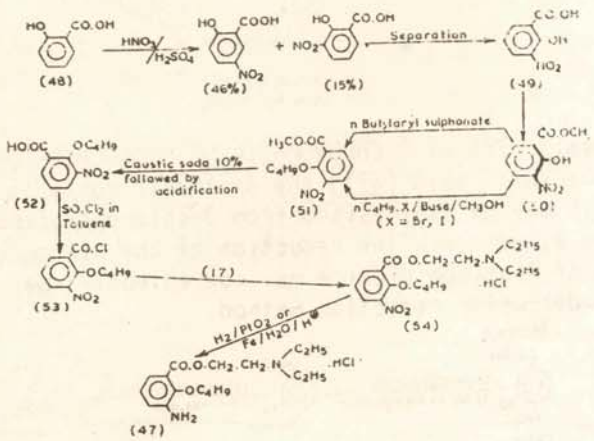
EDAN (4) (35) could be conveniently prepared by the esterification of aspirin (36) with diethylamino ethanol (17), using thionyl chloride.



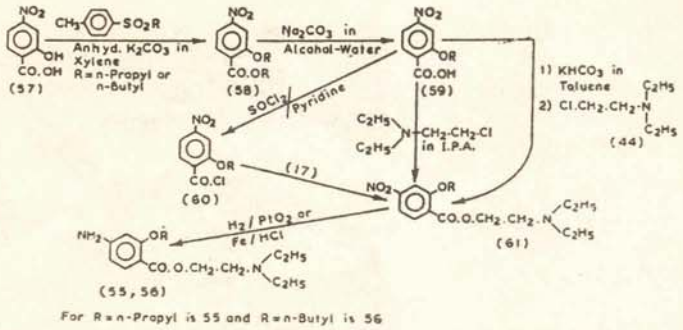
Synthesis (25) of PROPARACAINE (37) or BUTHOXYCAINE (38) requires 4-hydroxy benzoic acid (39) as the starting material. Nitration of p-hydroxybenzoic acid or its methyl/ethyl ester (40) followed by hydrolysis produces, the acid (39). Treatment of the latter with propyl p-toluene sulfonate (41) furnishes the ether-ester (42) which is safonified to the corresponding acid (43). Condensation of the acid with 2-diethylaminoethyl chloride (44) or treatment of the acid chloride of (43) with 2-diethylamino ethanol 17 gives the base (45) or its hydrochloride respectively. Iron-hydrochloric acid reduction of the nitro group of (45) yields (37). Replacement of (41) by n-butylaryl sulfonate (46) in above series of reactions furnishes (38). The starting compound (40) is produced (26) either from potassium phenolate and carbondioxide or by heating phenol with potassium ethyl carbonate.



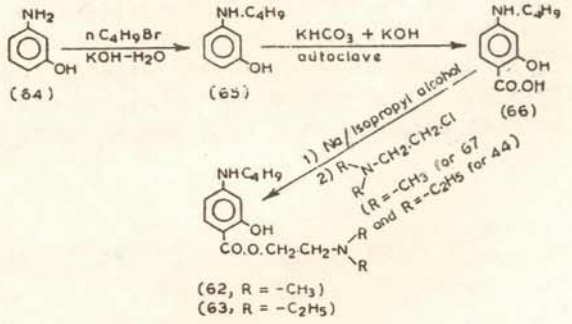
METABUTOXYCAINE HYDROCHLORIDE (47) is synthesised (27) employing salicylic acid (48) as the starting material. The latter on nitration yields 3-nitrosalicylic acid (49) as a minor component. Conversion of 49 into the corresponding methyl ester (50) followed by treatment with n-butyl bromide produces the ester-ether (51). The latter is also prepared from (50) according to the method of Clinton et al. by treatment with n-butylaryl sulfonate. Alkaline hydrolysis of the ester-ether (51) furnishes the corresponding acid (52). Conversion of the acid (52) into the acid chloride (53) followed by treatment of (53) with (17) produces the aminoalcohol ester (54) as the hydrochloride which is hydrogenated in presence of Platinum dioxide to yield (47). The reduction has also been effected with iron powder and water in a little acid.



Synthesis (25) of PROPODYCAINE (55) and AMBUCAINE (56) follows similar routes as those indicated for PROPARACAINE (37) using 4-nitrosalicylic acid (57) as the starting material as outlined below:

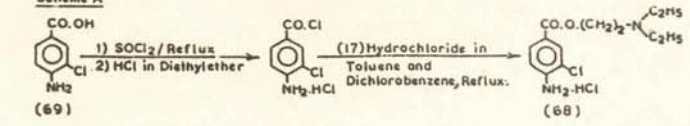


Both HYDROXYTETRACAINE (62) and 2- DIETHYLAMINOETHYL PARABNUTYLAMINO SALICYLATE (63) are synthesised (28) utilising m-aminophenol (64) as the starting material. The latter is N-butylated by treatment with n-butyl bromide in presence of potassium hydroxide to give (N-butyl) m-amino phenol (65); the latter on heating with potassium bicarbonate and potassium hydroxide under pressure is converted into (N-n-butyl)- 4-amino salicylic acid (66), which on treatment with one equivalent of sodium isopropoxide in isopropanol, and subsequent condensation with dimethyl amino ethyl chloride (67) or diethylamino ethyl chloride (44) produces (62) or (63) respectively. Compound (63) is no more in commercial use now.

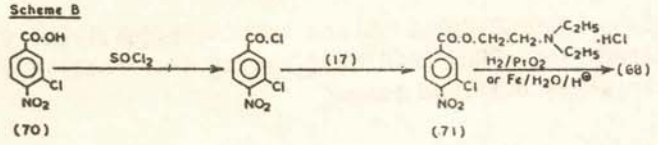


The synthesis (29) of 2-CHLOROPROCAINE HYDROCHLORIDE (68) starts with 4-amino 3-chlorobenzoic acid (69); the synthetic route is shown in Scheme A. Alternatively, it may be synthesised from 3-chloro-4-nitrobenzoic acid (70) as shown in scheme B. However, the reduction of the nitrogroup of 71 by hydrogen in presence of Platinum dioxide may conveniently be replaced by more cheaper iron powder-water reduction method.

Scheme A

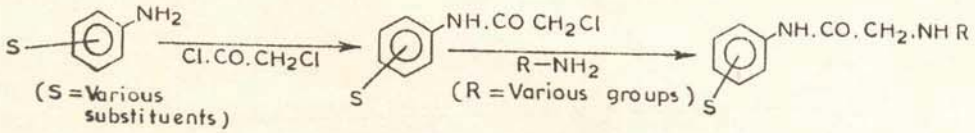


Scheme B



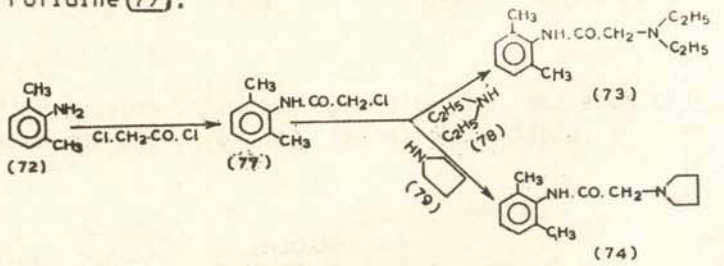
B. Compound represented by FORMULA -II (Amides):

The general preparation of this class involves the condensation of substituted aniline with haloacid chloride (usually chloroacetyl chloride), and subsequent treatment of the intermediate with an amine.



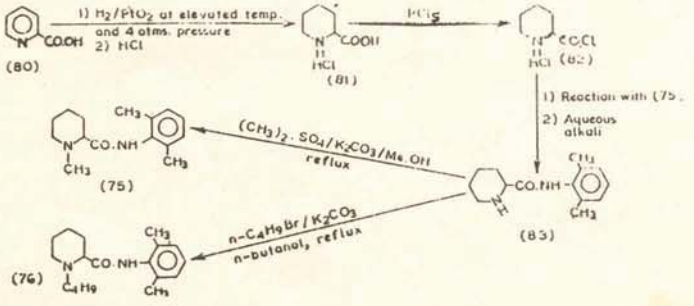
A number of derivates of 2,6 -dimethyl aniline(72) have been used as the amide type of local anaesthetics. Compounds which have been used commercially to a great extent are LIDOCAINE(73),PYRROCAINE(74). MEPIVACAINE(75)AND BUPIVACAINE(76).

The synthesis (30) of LIDOCAINE(73)is accomplished by acetylating (72) with chloroacetyl chloride and subsequently condensing the resultant product namely 2-chloro acetamido xylene(77)with diethyl amine(78). PYROCAINE(74) is synthesised (31) from the same aniline derivative(77)by condensing the latter with pyrrolidine(79).

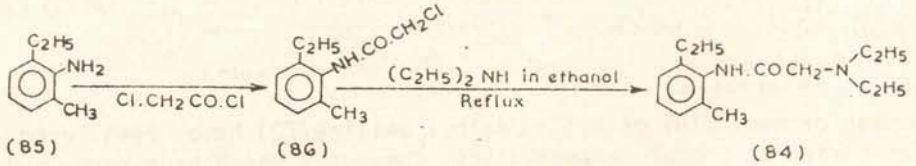


MEPIVACAINE (32)(75) and BUPIVACAINE (33) (76) are both synthesised starting from alpha picolinic acid(80).

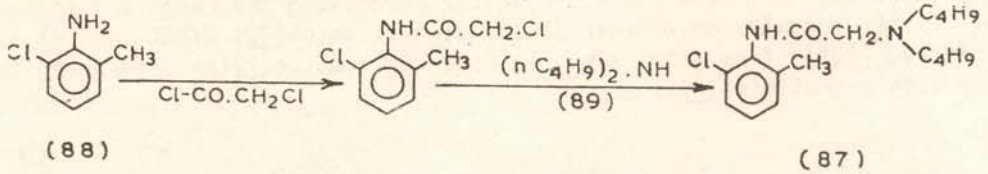
The starting acid(80)is conveniently prepared by permanganate or dichromate or nitric acid oxidation of alpha picoline. Picolinic acid(80)is hydrogenated at elevated temperature and low pressure and then treated with hydrogen chloride to yeild alpha picolinic acid hydrochloride(81). Conversion of(81) into its acid chloride(82)followed by treatment with (75) yields the basic amide (83). The amide on alkylation with dimethyl sulfate or butyl bromide furnishes(75)or(76)respectively.



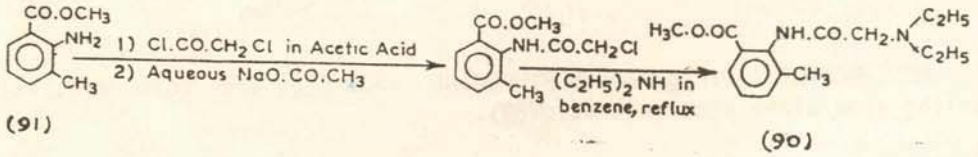
DIETHYLAMINOETHYL-6-ETHYLTOLUDINE (84) commonly known as GRAVOCAINE which is very similar to LIDOCAIENE(73)is synthesised (34) using routes similar to that followed for(73)and employs 2-ethyl-6-methylaniline(85) instead of (72). Chloroacetyl chloride reacts in cold condition with(85)and the resulting anilide(86)is reacted with diethylamine in ethanolic medium.



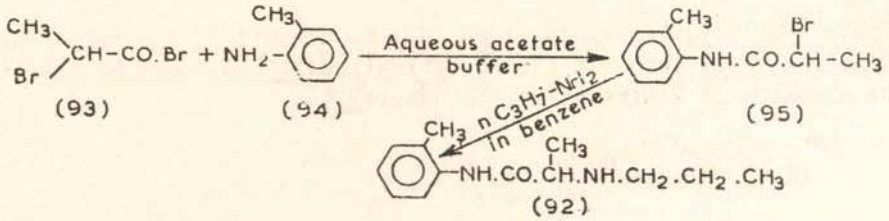
BUTANILICAINE(87)synthesis (35) is analogous to the above except that 2-chloro-6-methylaniline(88)is used in place of(85)and dibutylamine(89)is used instead of diethylamine.



TOLYCAINE(90) is made (36) by employing methyl 2-amino-3-methyl methylbenzoate (91) as the starting material and following the same routes as for LIDOCAINE(73).

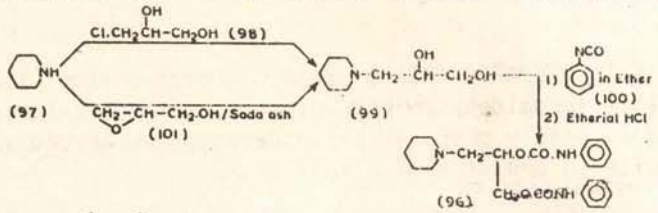


PRILOCAINE(92)is synthesised (37) by the condensation between alphabromo propionyl bromide(93)and 2-methyl aniline(94), thereafter heating the resultant amine(95)with n-propylamine in benzene.

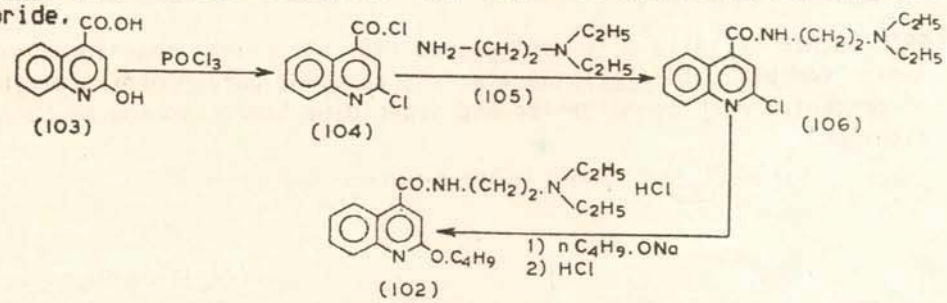


C. Local Anaesthetic Chemicals appended in Table III.

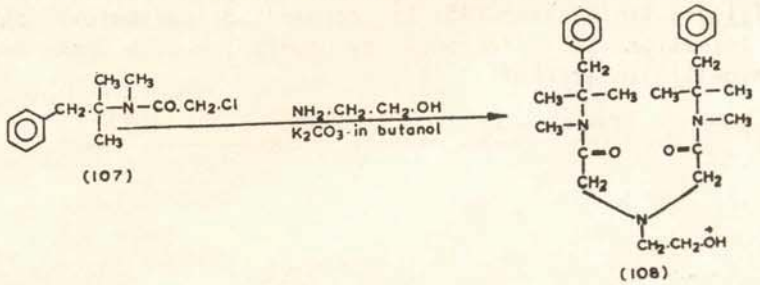
DIPERODON HYDROCHLORIDE(96)is obtai-ned (38) by condensing piperidine 97 with glyceryl chlorohydrin(98)in the presence of alkali, followed by treatment of resulting 1-piperidinopropan -2,3-diol(99)with phenyl isocynate (100) and preparing the hydrochloride thereof. The aminoalcohol(99)has also been (39) reported to be produced in high yield from piperidine and glycidol(101).



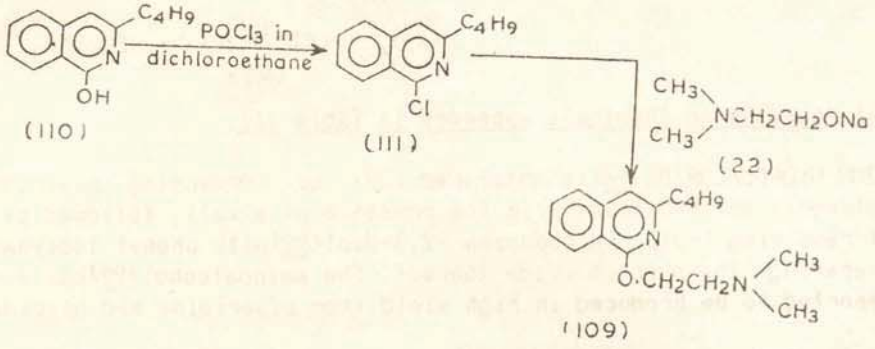
DIBUCAINE HYDROCHLORIDE(102)is synthesised (40) by converting 2-hydroxyquinoline 4-carboxylic acid(103)into the 2-chloro compound(104)and reacting (104)with N 1,1 -diethylethylenediamine(105)and thereafter heating the intermediate (106) with sodium butoxide. The base is then converted into the hydrochloride.



Condensation (41) between N-methyl N-trimethyl alpha-benzyl carbamoyl chloride(107)and alpha amino ethanol using potassium carbonate gives OXYTHAZAINE (108).

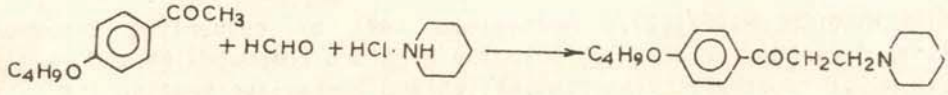


DIMETHISOQUIN(109) is synthesised (42) by converting 3-butyl 1-hydroxy isoquinoline (110) into its chloro derivative(111) followed by reacting(111) with the alkoxide of 2-dimethylaminoethanol(22).



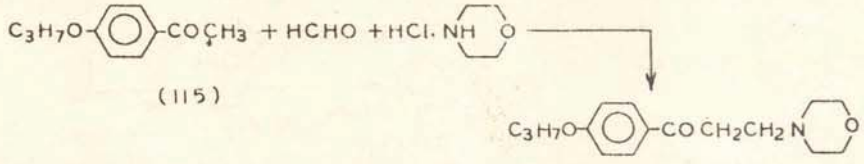
(110) (111) (22) (109)

DYCLONINE(112) IS PREPARED (43) by Mannich condensation of parabutoxy acetophenone (113), formaldehyde amd piperidine hydrochloride. The starting compound(113) is easily prepared by condensing parahydroxyacetophenone with n-butyl bromide in presence of alkali.



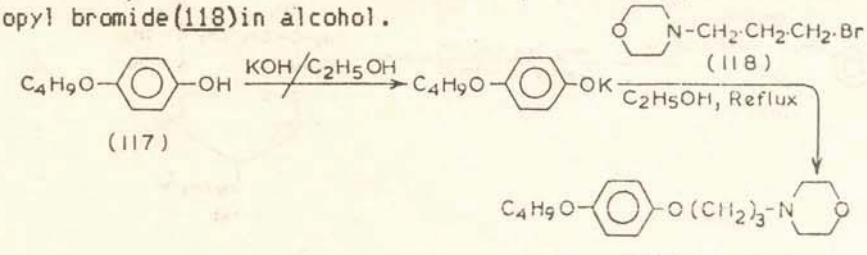
(113) (112)

PROPIPOCAIENE(114) is also synthesised (43) utilizing reactions similar to those for DYCLONINE(112); the starting compound para-propoxyacetophenone(115) is condensed with formuldehyde and piperidine hydrochloride by Mannich reaction.



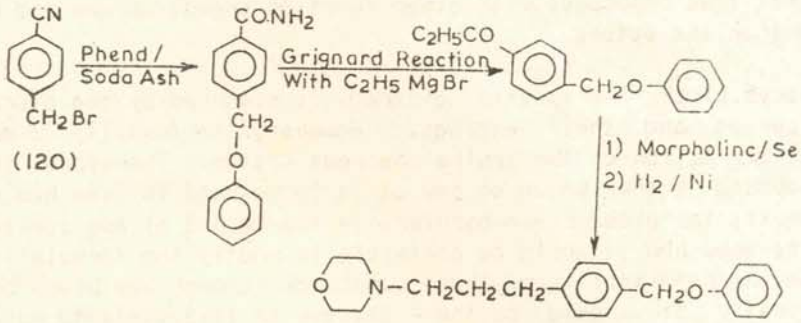
(115) (114)

PARAMOXINE(116) is synthesised (45) by converting parabutoxy phenol (117) into its potassium salt followed by refluxing with Gamma 4-morpholinyl propyl bromide(118) in alcohol.



(118) (117) (116)

FOMOCAINE(119)is conveniently synthesised (45) starting from 4-cyanobenzyl bromide(120)following the steps narrated below:



(119)

DISCUSSION AND CONCLUSIONS:

(a) Of all the compounds described above, Lidocaine has been most extensively used world-over. After its synthesis in 1948 by the Astra Group in Sweden many new compounds have been synthesised but none has so far been able to take over the popularity and commercial place of lidocaine. The reason is probably that the practicising anaesthetists world-over had greater access to the availability of the formulations of lidocaine than those of others, and the properties of lidocaine suited in its application in many situations of minor surgery, gynaecology and dentistry. The change over to other anaesthetic formulations was thus rather slow, though more efficacious products for specific applications had already been discovered.

(b) Of the 34 industrially used synthetic local anaesthetics discussed, 28 were esters and amides, and the remaining 6 compounds were imides, ketones and ethers. It seems thus that in the possibilities of succeeding to come out with better local anaesthetic formulation, one may first look for a choice from among local anaesthetic compounds having ester and amide linkages.

(c) The main complaint against the use of local anaesthetic compounds in general is that they are too toxic in nature. This is the main reason why many compounds discovered world over have not been commercialised. Compounds with relatively lower toxicity are lower in effectiveness as well. The efficacy of these compouds are exmined by measuring the duration of anaesthesia, the toxic effects produced and the concentration of the drug in blood plasma. After being injected, these drugs are distributed to all the organs

and therefore the plasma level decreases rapidly. The drugs are metabolised by enzymatic hydrolysis and the products of hydrolysis are exerted primarily through the kidney in the urine. Esters and amides are relatively easily metabolished than compounds with other function group; amides are metabolised slower than the esters.

(d) In nerve block, therapeutic efficacy is measured by the block of the specific nerves and their endings. However, the toxicity is manifested mainly by their action on the central nervous system. Therefore in search for a compound either known or new it is to be kept in view how each compound permeates the blood-brain barrier. In the method of application also, it is to be seen how it would be posssible to modify the formulations so as to minimise the permiability of these compounds through the blood-brain barrier. Ideally it should be the endeavour to take steps to maximise the concentration of the drug at the site where it should act and minimise the concentration at unwanted places and organs. Probably a carrier mediated approach such as a liposome, a specific nerve antibody or a poly electrotyle hooked anaesthetic compound would have to be looked for directing the anaesthetic compound to the specific application site. This is a major area of appropriate formulation development. Discussion on this is however beyond the scope of this paper.

(e) It is thus felt that among the relatively more toxic members, better compounds may be obtained from among amides and esters which are metabolised in the body at optimal rates. The optimum metabolic rate values are however to be established (4).

(f) The synthesis of these compounds are somewhat simpler. A well managed laboratory or a manufacturing unit having facilities of unit operations like oxidation, reduction, refluxing, distillation filtration, centrifugation, and vacuum or low temperature drying could easily venture to undertake the synthesis of these compounds. The starting chemicals required for the various synthesis are also easily available for purchase. Many of these could also be locally synthesised from simple basic chemicals like toluene, paranitro toluene, salicylic acid, chlorine, various alcohols, diethyl amine, ethylene oxide, 2,6-xylidine, chloro acetic acid, thionyl chloride etc. which are usually available abundantly in most of the industrially developed countries.

Opinions on the place of the specific local anaesthetics for the specific management of minor surgery vary among nations,,institutions and individuals. The standard texts provide adequately the descriptions about the techniques of nerve block; however the anaesthesists would have to acquire personal practical knowledge and form subjective opimion about these compounds through the use of specific anaesthetic chemicals in specific clinical situations. Many of the anaesthetics specially effective in certain

situations are not available world over. Drug manufacturers in every country could strengthen the hands of the anaesthesists by making them available the more potent and safer ones. It is anticipated that this review would be useful to the manufaturers to choose among the existing commercially available molecules for eventually taking up the synthesis of the more relevant ones on commercial scale. Though this is related with other factors such as the size of the local merket, the regional availability of relevant raw materials, the technological capabilities, the R&D back ups of companies as also the Patent Laws and the Drug Acts of the country, the review would work as the one important step to the willing manufacturers, who propose to plan and eventually go in for the manufacturing venture.

(g) A few drugs like Carticaine, Leucinocaine, Phenacaine, etc. not described here, have been used in limited quantities in some parts of the world. Some other potent candidate drugs which have not yet been marketed like GEA-968 (4), Pentacai-ne (4), YAU-17 (4) and Centbucridine (46) etc. are yet to score their marks and only the future would tell how they would fair in the competitive international market. Meanwhile, the search for newer and better anaesthetics would continue.

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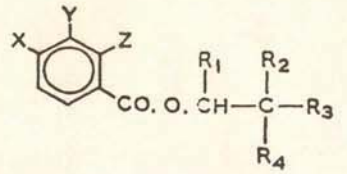
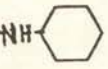
Table - I

(Local anaesthetics - esters)



(X, Y, Z, R_1, R_2, R_3, R_4 are various substituents as indicated in the table)

FORMULA-I (ESTERS)

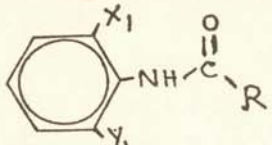
Sl. No.	X	Y	Z	R_1	R_2	R_3	R_4	Generic/ common name	Molecular formula (molecular wt.), used mainly as salt of acid with molecular formula	Main uses	Marketed by main company and Brand Name
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
1	-H	-H	-H	-H	-H	-H		PIPEROCAINE	$C_{16}H_{23}NO_2$ (261.37) As hydrochloride ($C_{16}H_{24}Cl.NO_2$)	With or without adrenaline in infiltration, surface, spinal and epidural anaesthesia.	Lilly (U.S.A.) as METYCAINE.
2.	-H	-H	-H	-H	$-CH_3$	$-CH_3$	$-NHC_3H_7$	MEPRYLCAINE	$C_{14}H_{21}NO_2$ (235.34) As hydrochloride ($C_{14}H_{22}Cl.NO_2$)	With adrenaline in dentistry. (Short duration of action).	Du Mont (U.S.A.) as CRACAINE.
3.	-H	-H	-H	$-CH_3$	-H	-H		HEXYLCAINE	$C_{16}H_{23}NO_2$ (261.35) As hydrochloride ($C_{16}H_{24}ClNO_2$)	With or without adrenaline in infiltration, surface and spinal anaesthesia. Rapid onset of action.	Merck Sharp & Dohme (U.S.A.) as CYCLAINE.
4.	$-NH_2$	-H	-H	-H	-H	-H	-H	ETHYLAMINO BENZOATE	$C_9H_{11}NO_2$ (165.19) As hydrochloride ($C_9H_{12}Cl.NO_2$)	As surface anaesthetic of mucous membrane skin and wounds.	Hoechst (India) as BENZOCAINE
5.	$-NH_2$	-H	-H	-H	-H	-H	$-N<^{C_2H_5}_{C_2H_5}$	PROCAINE	$C_{13}H_{20}N_2O_2$ (236.30) As hydrochloride ($C_{13}H_{21}ClN_2O_2$)	For nerve block and spinal anaesthesia. To relieve gastro-intestinal pain, used by mouth.	Hoechst (India) as NOVOCAIN

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
6.	$-NH.C_4H_9$	-H	-H	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	TETRACAINE	$C_{15}H_{24}N_2O_2$ (264.38) As hydrochloride ($C_{15}H_{25}ClN_2O_2$)	With or without adrenaline for surface, spinal and infiltration anaesthesia. Prolonged action.	Winthrop (U.S.A.) as PONTOCAINE
7.	$-NH_2$	-H	-H	-H	-H	-H	$-CH_2-N(C_4H_9)(C_4H_9)$	BUTACAINE	$C_{18}H_{30}N_2O_2$ (306.44) As sulfate ($C_{36}H_{62}N_4O_8S$)	For surface anaesthesia. Action rapid and prolonged.	Abbott (U.S.A.) as BUTYNSULFATE
8.	$-NH_2$	-H	-H	-H	-H	-H	$-NH-CH_2-CH(CH_3)(CH_3)$	BUTETHAMINE	$C_{13}H_{20}N_2O_2$ (236.30) As hydrochloride ($C_{13}H_{21}ClN_2O_2$)	With adrenaline for dental operations and other minor surgery. Potent but more toxic.	Philadelphia Lab (U.S.A.) as MONOCAINE
9.	$-OC_2H_5$	-H	-H	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	PARETHOXY-CAINE	$C_{15}H_{23}NO_3$ (265.34) As hydrochloride ($C_{15}H_{24}ClNO_3$)	Chiefly used to relieve pain of mucous membranes of larynx.	Delayrangl (France) as MAXICAINE
10.	-H	-H	$-O.CO.CH_3$	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	EDAN	$C_{15}H_{21}NO_4$ (279.34) As hydrochloride ($C_{15}H_{22}ClNO_4$)	Anaesthetic having analgesic and anti-inflammatory properties. More potent than procaine.	Polfa (Poland) as EDAN
11.	$-OC_3H_7$	$-NH_2$	-H	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	PROPARACAINE	$C_{16}H_{26}N_2O_3$ (294.38) As hydrochloride ($C_{16}H_{27}ClN_2O_3$)	Surface anaesthetic mostly used in ophthalmology.	Squibb (U.S.A.) as OPHTHAINE
12.	$-OC_4H_9$	$-NH_2$	-H	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	BETHOXYCAINE	$C_{17}H_{28}N_2O_3$ (308.41) As hydrochloride ($C_{17}H_{29}ClN_2O_3$)	Highly potent, rapid onset of action. Used for infiltration and in ophthalmology.	Millot (France) as MILLICAINE

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
13.	-H	$-NH_2$	$-OC_4H_9$	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	METABUTOXY-CAINE HYDRO-CHLORIDE	$C_{17}H_{29}ClN_2O_3$ (344.88)	Surface anaesthetic.	Novocol Chemical (USA) as PRIMACAINE
14.	$-NH_2$	-H	$-OC_3H_7$	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	PROPOXYCAINE HYDROCHLORIDE	$C_{16}H_{27}ClN_2O_3$ (330.86)	Used in dentistry alongwith other anaesthetics like Procaine to prolong anaesthesia.	Brench (U.S.A.) as BLOCAIN
15.	$-NH_2$	-H	$-OC_4H_9$	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	AMBUCAINE	$C_{17}H_{28}N_2O_3$ (308.41) As hydrochloride ($C_{17}H_{29}ClN_2O_3$)	Used in dentistry alone or with other anaesthetics.	Sterling Drug (U.S.A.) as STYPOCAINE
16.	$-NHC_4H_9$	-H	-OH	-H	-H	-H	$-N(CH_3)(CH_3)$	HYDROXYTETRA-CAINE	$C_{15}H_{24}N_2O_3$ (280.36) As hydrochloride ($C_{15}H_{25}ClN_2O_3$)	Topical anaesthetic used to relive pain of skin.	Hoechst (West Germany) as SALICAIN.
17.	$-NHC_4H_9$	-H	-OH	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	2-DIETHYLAMINO-ETHYL PARABUTYL-AMINO SALICYLATE	$C_{17}H_{28}N_2O_3$ ( ) As hydrochloride ($C_{17}H_{29}ClN_2O_3$)	Topical anaesthetic.	No more in commercial use.
18.	$-NH_2$	-H	-Cl	-H	-H	-H	$-N(C_2H_5)(C_2H_5)$	2-CHLORO-PROCAINE HYDROCHLORIDE	$C_{13}H_{20}Cl_2N_2O_2$ (307.22)	Twice as potent as Procaine. Used with adrenaline in infiltration and nerve block.	Pennwalt (U.S.A.) as NESACAINE

Table - II

(Local anaesthetics - Amides)



(X_1, Y_1 and R are various substituents as indicated in the table)

FORMULA-II(AMIDES)

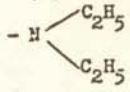
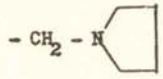
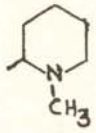
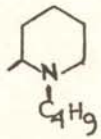
Serial No.	X_1	Y_1	R	Generic/Common name	Molecular Formula (Molecular weight) and used mainly as salt of acid with molecular formula	Main Uses	Marketed by main company and Brand Name
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
1.	$-CH_3$	$-CH_3$		LIDOCAINE	$C_{14}H_{22}N_2O$ (234.33) As hydrochloride ($C_{14}H_{23}ClN_2O.H_2O$)	Used in surface anaesthesia, infiltrations, blocks and spinal anaesthesia. Twice as potent as Procaine. Longer duration of action.	Astra (Sweden) as XYLOCAINE
2.	$-CH_3$	$-CH_3$		PYRROCAINE	$C_{14}H_2CN_2O$ (232.32) As hydrochloride ($C_{14}H_{21}Cl.N_2O$)	Similar to Lidocaine. Used for nerve block and infiltration in dentistry.	Graham Chem. Corpn. (U.S.A.) as DYNACAINE
3.	$-CH_3$	$-CH_3$		MEPIVACAINE	$C_{15}H_{22}N_2O$ (246.34) As hydrochloride ($C_{15}H_{23}Cl.N_2O$)	Used for nerve block, epidural and spinal anaesthesia. Action similar to Lidocaine.	Winthrop (U.S.A.) as CARBOCAINE
4.	$-CH_3$	$-CH_3$		BUPIVACAINE	$C_{18}H_{28}N_2O$ (288.43) As hydrochloride ($C_{18}H_{29}Cl.N_2O$)	Used in nerve blocks and epidural blocks. Used with or without adrenaline. Long acting and more potent than Lidocaine.	Winthrop (U.S.A.) as MARCAINE

Table II continued

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
5.	$-CH_3$	$-C_2H_5$	$-N(C_2H_5)(C_2H_5)$	DIETHYLAMINOETHYL 6-ETHYLTOLUIDINE	$C_{15}H_{24}N_2O$ As phosphate ($C_{15}H_{24}N_2O.H_3PO_4$)	Used in surface anaesthesia, infiltrations, blocks and spinal anaesthesia. Action similar to Lidocaine.	Bayer (West Germany) as CRAVOCAINE
6.	$-CH_3$	$-Cl$	$-N(C_4H_9)(C_4H_9)$	BUTANILICAINE	$C_{13}H_{19}ClN_2O$ (254.77) As hydrochloride ($C_{13}H_2O\ Cl_2N_2O$)	Used usually along with Procaine in dentistry and minor surgery. Short duration of action.	Hoechst (West Germany) as ECSTACAINE
7.	$-CH_3$	$-O.CO.CH_3$	$-N(C_2H_5)(C_2H_5)$	TOLYCAINE	$C_{15}H_{22}N_2O_3$ (278.34) As hydrochloride $C_{15}H_2$	Stronger than Procaine. Used in surface anaesthesia, infiltrations and nerve blocks.	Bayer (West Germany) as BAYCAIN
8.	$-CH_3$	$-H$	$-CH(CH_3)(NH-C_3H_7)$	PRILOCAINE	$C_{13}H_{20}N_2O$ (220.31) As hydrochloride ($C_{13}H_{21}ClN_2O$)	Used in surface anaesthesia, nerve block, infiltration and spinal anaesthesia. Used with or without adrenaline. Less toxic than Lidocaine.	Astra (Sweden) as CITANEST.

Table - III

(Anaesthetics other than Esters and Amides of Formulae I & II of Tables I & II respectively)

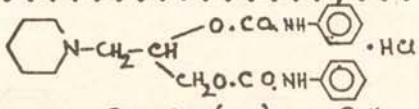
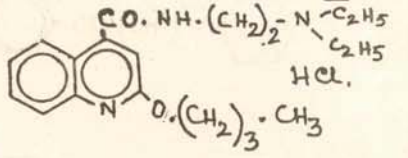
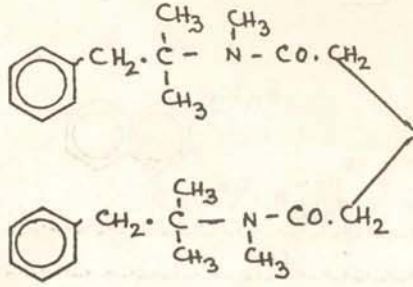
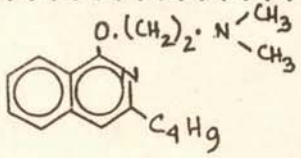
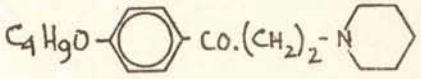
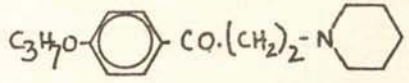
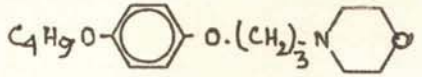
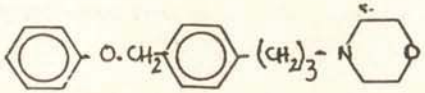
Serial No.	Generic/Common name	Chemical Structure	Molecular Formula (Molecular weight) and used mainly as salt of acid, with molecular formula	Main Uses	Marketed by mainly Company and Brand Name
(1)	(2)	(3)	(4)	(5)	(6)
1.	DIPERLON HYDROCHLORIDE		$C_{22}H_{28}ClN_3O_4$ (433.93)	Used as a surface anaesthetics in ointments and creams.	Merrel (U.S.A.) as PIOTHANE
2.	DIBUCAINE HYDROCHLORIDE		$C_{20}H_{30}Cl.N_3O_2$ (379.92)	Highly potent, about 20 times more active than Procaine. Used with adrenaline in spinal and infiltration anaesthesia. Toxicity limits application.	Geigy (U.S.A.) as NUPERCAINE
3.	CYETHAZAINE		$C_{28}H_{41}N_3O_3$ (467.63) As hydrochloride ($C_{28}H_{42}ClN_3O_3$)	Surface anaesthetic, highly potent with duration of action.	Wyeth (U.S.A.) as OXAINE

Table III continued.

(1)	(2)	(3)	(4)	(5)	(6)
4.	DIMETHISOQUIN		$C_{17}H_{24}N_2O$ (272.38) As hydrochloride ($C_{17}H_{25}ClN_2O$)	Used as surface anaesthesia in skin irritation pruritis etc.	Smith Kline (U.S.A.) as QUOTANE
5.	DYCLONINE		$C_{18}H_{29}NO_2$ (289.43) As hydrochloride ($C_{18}H_{28}ClNO_2$)	Used as surface anaesthesia. Onset of action is rapid.	Dow (USA) as DYCLONE
6.	PROPIPOCAINE		$C_{17}H_{25}NO_2$ (275.40) As hydrochloride ($C_{17}H_{26}ClNO_2$)	Used as surface anaesthesia in various painful states of skin and mucous membrane.	Germed (East Germany) as EXOTANCAIN
7.	PRAMOXINE		$C_{17}H_{27}NO_3$ (293.39) As hydrochloride ($C_{17}H_{28}ClNO_3$)	Used in surface anaesthesia on various painful conditions of Skin.	Abbot(U.S.A.) as TRONOTPANE
8.	POMOCAINE		$C_{20}H_{25}NO_2$ (311.43) As hydrochloride ($C_{20}H_{26}Cl.NO_2$)	Used in surface anaesthesia in various painful conditions of skin and mucous membranes.	Hermal (West German y) as ERBOCAIN