ACTA CHEMICA SCANDINAVICA 11 (1957) 1183—1190

Local Anaesthetics I.
N-Alkyl Pyrrolidine and N-Alkyl Piperidine Carboxylic Acid Amides

BO af EKENSTAM, BÖRJE EGNÉR and GÖSTA PETTERSSON

The research Laboratory, AB Bofors Nobelkrut, Bofors, Sweden

General methods and detailed examples are given for the preparation of 35 new aromatic amides of N-alkyl pyrrolidine and N-alkyl piperidine carboxylic acids. The compounds were prepared in order to test them as local anaesthetics. Pharmacological and clinical work has proved these compounds to be good local anaesthetics. The effect of compounds orginating from α-, β- and γ-carboxylic acids, respectively, compare as 7 : 2 : 1, while corresponding values for the toxicity compare as 2.7 : 1 : 1.

An extension of the N-alkyl group attached to the heterocyclic ring and an increase of the number of alkyl groups in the aromatic ring causes an increase in the effect as well as in the toxicity. The introduction of alkoxygroups in the aromatic ring lowers the toxicity but causes an increase in the irritation of living tissue. Alkylation of the amidic nitrogen as well as the introduction of an alkyl group between the amide and the aryl group decreases the effect. There appears to be no difference in pharmacological respect between the optical isomers.

dl-N-Methyl pipecolic acid 2,6-xylidide (Carbocaine) has proved suitable for clinical use.

In a number of papers [1-9], covering a period of some fifty years, local anaesthetics of amide type have been described. Though, as far as we know, no compounds were prepared where the carbonyl group of the amide was directly linked to one of the carbon atoms in a saturated or partly saturated heterocyclic ring.

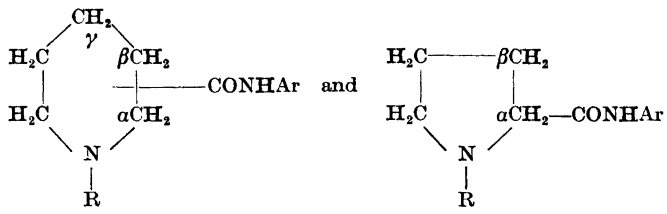
As it could be of interest to test compounds of this type, a number of aryl amides were synthesized starting from pyrrolidine and piperidine carboxylic acids.

A juxtaposition of the compounds prepared is given in Table 1. Their structure is apparent from the formulae.

Table 1

No.	Ar	R	Mol.weight	Melting point °C Base	Hydrochloride
		dl-N-Alkyl pipecolic acid amides			
1	C_6H_5	C_2H_5	232.15	108–110	186–188
2	C_6H_5	n-C_4H_9	260.17	83–84	158–160
3	C_6H_4, 2-CH_3	C_2H_5	246.16	97–98	224–225
4	C_6H_4, 2-CH_3	n-C_4H_9	274.18	oil	213–215
5	C_6H_4, 3-CH_3	C_2H_5	246.16	50–52	140–143
6	C_6H_4, 4-CH_3	C_2H_5	246.16	88–90	224–226
7	C_6H_3, 2,4-$(CH_3)_2$	C_2H_5	260.17	59–60.5	241–243
8	C_6H_3, 2,6-$(CH_3)_2$	CH_3	246.16	150–151	262–264
9	C_6H_3, 2,6-$(CH_3)_2$	C_2H_5	260.17	132–133	252–254
10	C_6H_3, 2,6-$(CH_3)_2$	n-C_3H_7	274.18	121	262
11	C_6H_3, 2,6-$(CH_3)_2$	n-C_4H_9	288.19	107.5–108	258.5
12	C_6H_3, 2,6-$(CH_3)_2$	*cyclo*-C_5H_9	300.20	158	268–269
13	C_6H_3, 2-Cl-6-CH_3	C_2H_5	280.61	101	261–261.5
14	C_6H_4, 2-C_2H_5	C_2H_5	260.17	94–95	234–235
15	C_6H_4, 4-OC_2H_5	C_2H_5	276.17	120	174–176
16	C_6H_3, 2-CH_3-4-OC_4H_9	CH_3	304.19	96–97	177
17	C_6H_2, 2,6-$(CH_3)_2$-4-OC_4H_9	CH_3	328.21	85–87	221–223
18	C_6H_2, 4,6-$(CH_3)_2$-2-OC_4H_9	C_2H_5	342.22	85–86	234–236
19	C_6H_2, 2,4,6-$(CH_3)_3$	C_2H_5	274.18	117	271–272.5
20	$C_6H_5CH_2$	CH_3	231.15	80–81	200–203
21	C_6H_5*	CH_3	246.16	oil	184–186
		dl-N-Alkyl nipecotic acid amides			
22	C_6H_3, 2,6-$(CH_3)_2$	CH_3	246.16	154–155	193–195
23	C_6H_3, 2,6-$(CH_3)_2$	C_2H_5	260.17	145	233–235
24	C_6H_3, 2,6-$(CH_3)_2$	n-C_3H_7	274.18	136–137	196–197
25	C_6H_3, 2,6-$(CH_3)_2$	*iso*-C_3H_7	274.18	157–158	219–220
26	C_6H_3, 2,6-$(CH_3)_2$	n-C_4H_9	288.19	114–115	207–208
27	C_6H_3, 2-Cl-6-CH_3	C_2H_5	280.61	122–123	223–224
28	C_6H_2, 2,6-$(CH_3)_2$-4-OC_2H_5	CH_3	290.18	110–112	oil
29	C_6H_2, 4,6-$(CH_3)_2$-2-OC_2H_5	CH_3	290.18	127–128	192–193
		N-Alkyl isonipecotic acid amides			
30	C_6H_5	CH_3	218.14	140–142	254–255
31	C_6H_3, 2,6-$(CH_3)_2$	C_2H_5	260.17	181–182	247–248
		dl-N-Alkyl proline amides			
32	C_6H_3, 2,6-$(CH_3)_2$	CH_3	232.15	68–70	215–217
33	C_6H_3, 2,6-$(CH_3)_2$	C_2H_5	246.16	91–93	235–237
34	C_6H_3, 2,6-$(CH_3)_2$	n-C_3H_7	260.17	110–112	257–258
35	C_6H_3, 2-Cl-6-CH_3	n-C_4H_9	294.62	77–78	233–235

* Amide nitrogen also ethylated



Yet in No. 20 a methylene group has been introduced between NH and Ar, and in No. 21 an alkyl group has been coupled to the amidic nitrogen.

For the preparation of these compounds there are several possible ways; only the most suitable will be described here. In the following survey of the methods there is for every reaction a roman numeral which refers to the corresponding description in the experimental part.

Method A. A pyridine carboxylic acid is transferred into an aryl amide (I), which is then catalytically (II) hydrogenated and alkylated at the ring nitrogen (III). (I) is most conveniently carried out over the acid chloride, which is prepared by treating a suspension of the sodium salt in toluene with phosphorus pentachloride. The hydrogenation was carried out according to a method by Barnes [10] for the preparation of piperidine carboxylic acid esters. The pressure was however kept at 4—5 atm and the temperature at *ca.* 80°. The alkylation is easily carried out according to common methods.

The pyrrole carboxylic acid amide cannot be hydrogenated in this way.

Method B. The amides of the saturated carboxylic acids (IV) are prepared before (V) or after (VI, VII) the alkylation of the ring nitrogen. (V) was carried out over the acid chloride, which was prepared according to Fischer [11] in acetyl chloride with phosphorus pentachloride. It should be observed that for a complete reaction piperidine carboxylic acid requires a temperature of 35°, while the formation of prolyl chloride according to Fischer occurs at 0°. This causes a racemization during the preparation of the amide from optically active pipecolic acid, while the amide of *l*-proline can be prepared with unchanged optical activity. N-Alkylated piperidine carboxylic acids were preferably prepared by alkylation and hydrolysis of the corresponding ester. β- and γ-Amides are easily prepared *via* the acid chlorides, which are obtained by treating the acids with thionyl chloride (VI). The acid chlorides of the α-carboxylic acids cannot be prepared in this way. The amides of these can also be prepared by treatment with *iso*cyanate (VII).

Method C. By modifying methods given by Albertson *et al.*[12] and Putochin [13] for the synthesis of proline, the heterocyclic nitrogen ring was obtained by ring closure as the last step before the N-alkylation. Thus an acid with the formula $H_2N \cdot (CH_2)_n \cdot CHClCOOH$ was prepared according to Albertson and thereafter transferred into an arylamide. Ring closure was then achieved in alkaline environment (VIII). The method of Putochin was modified so that as the first step one of the carbonyl groups in diethyl malonate was reacted with the desired arylamine to give a monoamide according to Chattaway and Olmsted [14] (IX). The synthesis was continued essentially according to Putochin. From the monoaryl amide the *iso*nitroso compound (X) was prepared,

nitrosylchloride being used as nitrosating agent as suggested by Whiteley [15]. After reduction to amine (XI), this was reacted with alkylene dibromide, whereafter ring closure was achieved in strongly acid environment (XII).

Only α-compounds were prepared according to method C. Tetrahydro quinaldinic acid amides and tetrahydro *iso*quinaldinic acid amides were also prepared according to the methods A—B. In a forthcoming communication an account will be given of these compounds.

In order to investigate if there was any difference in pharmacological respect between the optical isomeres of the α- and β-compounds *l*- and *dl*-N-ethyl proline 2,6-xylidide was synthesized. In addition *dl*-N-methyl pipecolic acid 2,6-xylidide was separated into its optical isomeres with the aid of tartaric acid.

PHARMACOLOGY

A full account of the pharmacological characteristics of the substances will be published elsewhere. However, some results of general interest will be reported here. Thus it has been established that the α-amides possess the best local anaesthetic effect. Derivatives where R was C_2H_5 and Ar was C_6H_3-2,6-$(CH_3)_2$ (Nos. 9, 23 and 31 in Table 1) and where the only difference was in the amide position were compared at blockage of *N. ulnaris*. With respect to duration α-, β- and γ-derivatives compared roughly as 7 : 2 : 1. The corresponding proline amide gave approximately the figure 3. These results agree well with the observation of Erdtman and Löfgren [5] of a decreasing effect in the amide series of aliphatic amino acids with an increasing distance between the amide and amino groups. β- and γ-Amides turned out to have about the same toxicity while the α-amide was 2.7 times as toxic. As, however, the effect is manifolded the α-amides appear to possess a better therapeutic index.

At weal tests and determination of LD_{50} on mice no statistical difference could be established between the two optical isomers.

An extension of the heterocyclic hydrocarbon chain R results in an increase in effect at the same time as the toxicity is aggravated. N-Alkyl-proline amides have a lower effect than the corresponding pipecolic acid amides even if the shortening of the hydrocarbon chain in the heterocyclic ring is considered. Alkylation of the arylamide nitrogen (No. 21) and the introduction of an alkyl group between the amide and aryl groups (No. 20) appear to decrease the local anaesthetic power.

The introduction of side chains into the aryl group cause an increase both in effect and toxicity. The replacement of an alkyl chain in the aryl group by an alkoxy group causes a decrease in the toxicity but makes the substance irritating on living tissues. Replacement of the group by chlorine increases the toxicity while the effect decreases.

The one for clinical use most suitable compound appeared to be No. 8, *dl*-N-methyl pipecolic acid 2,6-xylidide. The compound was given the name Carbocain and has been subjected to pharmacological examination by Ulfendahl [16] and to clinical by Dhunér *et al.* [16, 17]

The toxicity values for some comparable derivatives are summarised in Table 2.

Table 2.

No. in Table 1				R	Ar	LD_{50} on mice, mg/kg			
α	*β*	*γ*	prolyl			*α*	*β*	*γ*	prolyl
8	22			CH_3	C_6H_3, 2,6-$(CH_3)_2$	43.3	84.3		
9	23	31	33	C_2H_5	C_6H_3, 2,6-$(CH_3)_2$	24.5	68.0	67.8	37.9
10	24		34	*n*-C_3H_7	C_6H_3, 2,6-$(CH_3)_2$	13.5	37.9	—	22.3
	25			*iso*-C_3H_7	C_6H_3, 2,6-$(CH_3)_2$	—	30.5		
11	26			*n*-C_4H_9	C_6H_3, 2,6-$(CH_3)_2$	12.7	20.2		
13	27			C_2H_5	C_6H_3, 2-Cl-6-CH_3	16.9	38.3		
1				C_2H_5	C_6H_5	60.4			
3				C_2H_5	C_6H_4, 2-HC_3	36.7			
15				C_2H_5	C_6H_4, 4-OC_2H_5	51.7			
12				*cyclo*-C_5H_9	C_6H_3, 2,6-$(CH_3)_2$	4.6			
19				C_2H_5	C_6H_2, 2,4,6-$(CH_3)_3$	26.8			
17				CH_3	C_6H_2, 2,6-$(CH_3)_2$-4-*n*-OC_4H_9	38.0			
		30		CH_3	C_6H_5				

EXPERIMENTAL

A description of the synthesis of every compound in Table 1 is not given. However, an account is rendered below of all the methods mentioned in the introduction.

Iso*nicotinic acid 2,6-xylidide (I)*. *Iso*nicotinic acid sodium salt (145 g) was suspended in toluene (550 ml) and phosphorus pentachloride (80 g) added. After 1 h at 90° the solution was filtered, and 2,6-xylidine (120 g) added drop by drop to the filtrate under vigorous stirring. The precipitate was drawn off on a funnel, and washed with toluene and ether to give the hydrochloride as white crystals. Yield 210 g (93 %); m.p. 250—251°C. The hydrochloride (150 g) was dissolved in water (500 ml), carbon treated and precipitated with NaOH. Yield 123 g (95 %); m.p. after recrystallization from alcohol and ether 154—155°C. (Found: N 12.27. Calc. for $C_{14}H_{14}ON_2$: N 12.39).

Iso*nipecotic acid 2,6-xylidide (II)*. *Iso*nicotinic acid 2,6-xylidide (36 g) was dissolved in abs. alcohol (100 g) and acetic acid (20 g) and hydrogenated in the presence of platinum oxide (0.5 g) at 80° and *ca.* 4 atm. The catalyst was filtered off and to the filtered solution was added 50 % caustic soda lye (27 g) and ether (150 ml). After filtering off, precipitated sodium acetate the solution was evaporated to dryness under vacuum. The residue was dissolved in diluted hydrochloric acid, carbon treated and the base was precipitated with NaOH. Yield 33 g (89 %); m.p. after recrystallization from alcohol and ether 181—182°C. (Found: N 11.99. Calc. for $C_{14}H_{20}ON_2$: N 12.07).

N-Ethyl iso*nipecotic acid 2,6-xylidide (III)*. *Iso*nipecotic acid 2,6-xylidide (50 g) was heated on a steambath together with diethyl sulphate (100 g) for 30 min. Complete dissolution was obtained. After cooling down, the solution was washed with water (400 ml). The layer consisting of unreacted diethyl sulphate was separated and washed with a further lot of water (100 ml). The combined water phases were washed with ether (3 × 200 ml), the remaining ether removed from the water solution and this was then treated with carbon. The reaction product was precipitated with NaOH. Yield 53 g (92 %); m.p. after recrystallization from alcohol 181—182°C (gives a depression with unalkylated product). (Found: N 10.71. Calc. for $C_{16}H_{24}ON_2$: N 10.77).

dl-Pipecolic acid hydrochloride (IV). Picolinic acid (70 g) was dissolved in abs. alcohol (300 g) and acetic acid (70 g) and hydrogenated in the presence of platinum oxide (1 g) at *ca.* 80°C and 4—5 atm. When no more hydrogen was absorbed (after 1,5—2 h), the mixture was cooled and filtered. Conc. hydrochloric acid (60 g) was added to the filtrate and cooled to —20°C. Yield 75 g (80 %); m.p. 262—264 °C. (Found: Cl 21.40. Calc. for

$C_6H_{12}O_2NCl$: Cl 21.42). By evaporating the mother liquor to dryness more product was obtained. The total yield amounted to 92—95 %.

dl-Pipecolic acid 2,6-xylidide (V). *dl*-Pipecolic acid hydrochloride (100 g) was suspended in acetylchloride (1 000 ml). Phosphorus pentachloride (100 g) was added under vigorous agitation. After a reaction time of 8 h at 35° with a second addition of phosphorus pentachloride (50 g) after 6 h the mixture was cooled to 10—15° and filtered. The precipitate was washed with toluene and acetone and suspended in acetone (600 ml). All in one 2,6-xylidine (180 g) was added under stirring. The mixture was heated to boiling for 30 min. After cooling the precipitate formed was drawn off and washed with acetone and dryed. In order to remove remaining xylidine the product was steam distilled at pH 5.5, carbon treated and precipitated with NaOH. Yield 112 g (80)); m.p. 116—117°. After recrystallization from alcohol the m.p. rose to 121°. (Found: N 12.03. Calc. for $C_{14}H_{20}ON_2$: N 12.07).

dl-N-Methyl pipecolic acid 2,6-xylidide (III). *dl*-Pipecolic acid 2,6-xylidide (100 g) was dissolved in methyl alcohol (200 ml) and potassium carbonate (45 g) added. Dimethyl sulphate (55 g) was added under stirring, and the mixture refluxed for 6 h. After cooling the mixture was filtered, and the filtrate evaporated to dryness. The residue was dissolved in conc. hydrochloric acid (37 ml) and water (750 ml), carbon treated and precipitated with NaOH. Yield 80.5 g (76 %); m.p. 148°C. After recrystallization from ether the m.p. rose to 150—151°C. (Found: N 11.37. Calc. for $C_{15}H_{22}ON_2$: N 11.38).

dl-Proline-2-chloro-6-methyl anilide (V). To a suspension of the hydrochloride of *dl*-prolinechloride (prepared according to Fischer [11]) (5 g) in acetone (30 ml) 2-chloro-6-methyl aniline (10 g) was added. The mixture was heated on a water bath for 30 min. Water was added until complete solution of any precipitate formed, and the acetone driven off under vacuum. The pH of the solution was adjusted to 5 and the excess of amine removed by extraction with ether. The water solution was made strongly alkaline with NaOH, and the base then extracted with ether. After drying the ether solution with sodium sulphate the ether was evaporated, and *dl*-proline 2-chloro-6-methyl anilide was obtained as an oil. Yield 6 g (85,5 %). (Found: N 11.63. Calc. for $C_{12}H_{15}ON_2Cl$: N 11.74).

dl-N-n-Butyl proline 2-chloro-6-methyl anilide (III). *dl*-Proline 2-chloro-6-methyl anilide (6 g) was dissolved in *n*-butyl alcohol (30 ml) and then under stirring refluxed with potassium carbonate (3 g) and *n*-butyl bromide (3.6 g) for 20 h. The reaction mixture was filtered and the filtrate evaporated under vacuum. The residue was dissolved in diluted hydrochloric acid and carbon treated. A crystalline precipitate was obtained with NaOH. Yield 6 g (81 %); m.p. after recrystallization from ether 77—78°C. (Found: N 9.41. Calc. for $C_{16}H_{23}ON_2Cl$: N 9.52).

dl-N-Ethyl nipecotic acid 2-chloro-6-methyl anilide (VI). *dl*-N-Ethyl nipecotic acid (50 g) was treated with thionyl chloride (150 g). When the reaction subsided, the mixture was heated on a water bath for 30 min, when a clear solution was obtained. The excess of thionyl chloride was driven off under vacuum, until crystallization occurred. In order to make the crystallization complete, ether (100 ml) was added and the mixture shaken, after which the crystal slurry was drawn off and washed with ether. Without drying the crystals were suspended in acetone (300 ml). To the suspension 2-chloro-6-methyl aniline (65 g) was added drop by drop. The mixture was refluxed for 15 min after which the acetone was driven off under vacuum. The residue was dissolved in water (500 ml). The pH was adjusted to 5.5 and unreacted 2-chloro-6-methyl aniline removed by ether extraction. The water solution was cleared from ether and the base precipitated with NaOH. Yield 75 g (84 %); m.p. after recrystallization from alcohol and ether 122—123°C. (Found: N 9.99. Calc. for $C_{15}H_{21}ON_2Cl$: N 9.98).

dl-N-Ethyl pipecolic acid o-toluidide (VII). *dl*-N-Ethyl pipecolic acid (50 g) was heated on a steam bath under stirring with 2-methyl phenyl *iso*cyanate (100 g). When the evolution of carbon dioxide had ceased the excess of *iso*cyanate was driven off under vacuum. The residue was boiled for 15 min with 27 ml of conc. hydrochloric acid and 250 ml of water. The mixture was cooled down and filtered. After carbon treatment and precipitation with NaOH the base was obtained in the form of crystals. Yield 52 g (65 %); m.p. after recrystallization 97—98°C. (Found: N 11.40. Calc. for $C_{15}H_{22}ON_2$: N 11.38).

dl-Proline 2,6-xylidide (VIII). 2-Chloro-5-aminovaleric acid hydrochloride (94 g) prepared according to Albertson *et al.*[12] was chlorinated in acetyl chloride (450 ml) with phosphorus pentachloride (188 g) under cooling with ice water. After 7 h the crystals

formed were washed with toluene and suspended in acetone. 2,6-Xylidine (120 g) was added to the suspension, and the mixture heated on a water bath for 30 min. Water was added and the acetone driven off under vacuum. The pH was adjusted to 5 and the excess of xylidine removed by ether extraction. The water solution was carbon treated and NaOH added to pH 12, when an oil began to precipitate. After stirring for 2 days at room temperature a crystalline product was formed. This was extracted with ether, and after evaporation of the ether an oil was obtained which crystallized after some time. Yield 53.5 g (49 %). (Found: N 12.71. Calc. for $C_{13}H_{18}ON_2$: N 12.84).

After ethylation with diethyl sulphate according to III, a product was obtained, identical with *dl*-N-ethyl proline 2,6-xylidide prepared from *dl*-proline.

Malonic acid ethylester 2,6-xylidide (IX). 2,6-Xylidine (121 g) was heated with diethyl malonate (400 g) at 155—160° for 1 h and the ethanol distilled off as it was formed. Then the excess of diethyl malonate was distilled off under vacuum. To the crystalline residue ethanol (500 ml) was added. After cooling down the crystals of malonic acid dixylidide formed were filtered off. The alcohol solution was diluted with water (2 l) under agitation, when malonic acid ethylester xylidide crystallized out. The monoxylidide was filtered, washed with water and recrystallized from 50 % ethyl alcohol. Yield 138 g (58.8 %); m.p. 100—101°C. (Found: N 6.08. Calc for $C_{13}H_{17}O_3N$: N 5.96.)

Isonitrosomalonic acid ethylester 2,6-xylidide (X). To a solution of malonic acid ethylester 2,6-xylidide (60 g) in chloroform (400 ml) nitrosyl chloride was added during 6 h at 0°C. The crystals of the *iso*nitroso compound formed were filtered off washed with chloroform and dryed in vacuum. Yield 56 g. From the mother liquor a further 5 g were obtained by vacuum evaporation. Total yield 61 g (90.5 %); m.p. 193—194°C. (Found: N 10.51. Calc. for $C_{13}H_{16}O_4N_2$: N 10.60).

Aminomalonic acid ethylester 2,6-xylidide (XI). *Iso*nitrosomalonic acid ethylester 2,6-xylidide (60 g) was dissolved in formic acid (200 ml). Zinc powder (36 g) was added in portions during 1 h at 90—95°. After a further hour at 90° the hot solution was filtered and evaporated under vacuum. The evaporation residue was dissolved in hot amyl alcohol, washed neutral with 5 % bicarbonate solution and filtered. The amyl alcohol was driven off under vacuum and the residue recrystallized from 50 % ethyl alcohol. Yield: 47.2 g (83 %); m.p. 195°C. (Found: N 11.18. Calc. for $C_{13}H_{18}O_3N_2$: N 11.20).

dl-Pipecolic acid 2,6-xylidide (XII). In a sodium ethylate solution, prepared by dissolving sodium (4.6 g) in abs. alcohol (125 ml), aminomalonic acid ethylester 2,6-xylidide (50 g) was dissolved. Tetramethylene dibromide (87 g) was added at 70° during 20 min. The reaction mixture was then refluxed for 6 h, cooled down and filtered. The ethanol and excess of tetramethylene dibromide were distilled off with steam. The remaining oil was separated from the water and refluxed with conc. hydrochloric acid (150 ml) for 3 h, after which the solution was evaporated to dryness under vacuum. The residue was dissolved in water and the pH adjusted to 5 with caustic soda. The water solution was extracted with ether, carbon treated and precipitated with NaOH at pH 13. Yield: 16 g (34.5 %). M.p. 115—116°C. After recrystallization from ethyl alcohol the m.p. rose to 120—121°C. (Found: N 11.98. Calc. for $C_{14}H_{20}ON_2$: N 12.07).

REFERENCES

1. Einhorn, A. and Oppenheimer, M. *Ann.* **311** (1900) 154.
2. Einhorn, A. and Uhlfelder, E. *Ann.* **371** (1910) 162.
3. Miescher, K. *Helv. Chim. Acta* **15** (1932) 163.
4. Erdtman, H. and Löfgren, N. *Svensk Kem. Tidskr.* **49** (1937) 163.
5. Löfgren, N. *Arkiv Kemi Mineral. Geol.* **22A** (1946) No. 18.
6. Garmid, K. N., Ray, J. N. and Yajnik, J. N. *J. Indian Chem. Soc.* **17** (1940) 400.
7. Garmid, K. N., Ray, J. N. and Sarni, B. *J. Indian Chem. Soc.* **17** (1940) 619.
8. Hofstetter, E. *Nature* **170** (1952) 980.
9. Ehrhardt, G., Ruschiz, H., Stein, L. Anmüller, W. and Ther, L. Ger. 942993.
10. Barnes, A. *J. Am. Chem. Soc.* **49** (1927) 1308.
11. Fischer, E. och Reif, G. *Ann.* **363** (1908) 123.
12. Albertson, N. F. and Fillman, J. L. *J. Am. Chem. Soc.* **71** (1949) 2819.

13. Putochin, N. J. *Ber.* **56** (1923) 2213.
14. Chattaway, F. D. and Olmsted, J. M. D. *J. Chem. Soc.* **97** (1910) 939.
15. Whiteley, M. A. *J. Chem. Soc.* **83** (1903) 29.
16. af Ekenstam, B., Egnér, B., Ulfendahl, H., Dhunér, K. G. and Oljelund, O. *Brit. J. Anaesthesia* **11** (1956) 503.
17. Dhunér, K. G., Oljelund, O. and Aageson, G. *Acta Chir. Scand.* **1957**. *In Press.*

Received April 8, 1957.