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Syntheses of three Xylocaine® Analogues

Steric Effects in the Reaction between 2,6-Dimethylphenyllithium and Epichlorohydrin

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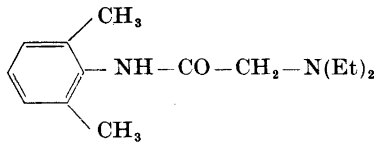
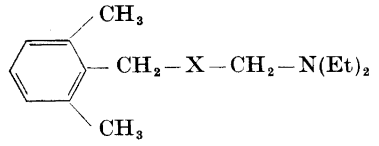
Three new compounds of the general structure $2,6\text{-}(CH_3)_2C_6H_3-CH_2-X-CH_2-N(C_2H_5)_2$, in which X represents CO, CH(OH) or CH_2 have been synthesized and examined for their sedative and local anesthetic actions. One intermediary formed compound, *i.e.* 3-(2,6-dimethylphenyl)-1,2-epoxypropane, was obtained anomalously from the reaction between 2,6-dimethylphenyllithium and epichlorohydrin. A simple explanation of the anomaly is given.

In this work, three new compounds (I–III) resembling Xylocaine®



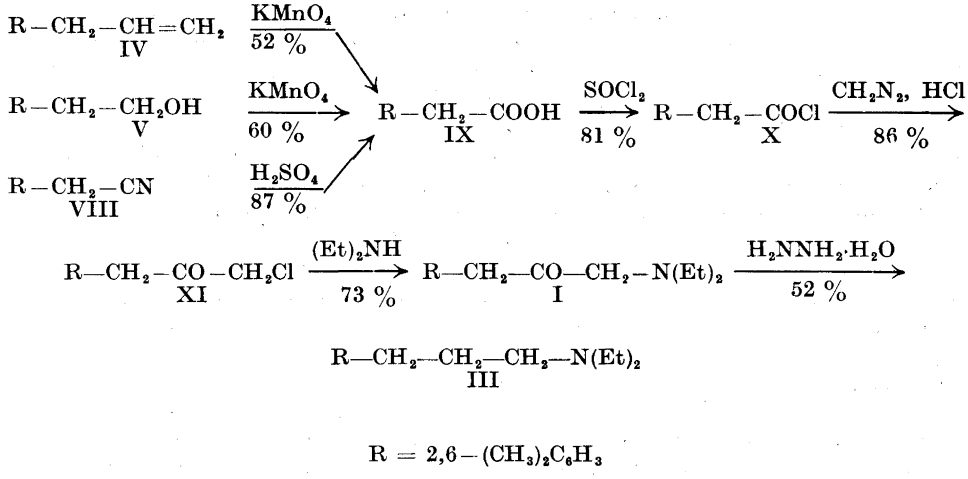
have been synthesized and tested pharmacologically. The compounds are of the general type



in which X is CO (I), CH(OH) (II) or CH_2 (III), *i.e.* the compounds are: 1-diethylamino-3-(2,6-dimethylphenyl)-2-propanone (I), 1-diethylamino-3-(2,6-dimethylphenyl)-2-propanol (II) and 1-diethylamino-3-(2,6-dimethylphenyl)-propane (III).

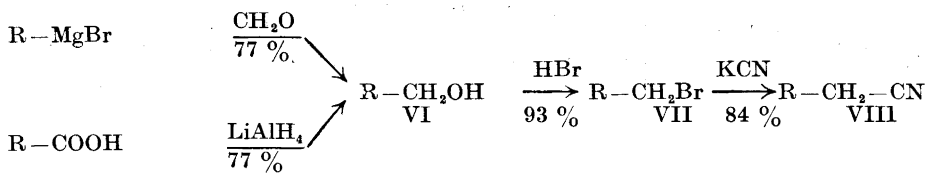
Compounds I and III were synthesized as outlined in Chart 1 or Chart 2.

Chart 1.



To Chart 1 the following additional details are given: 3-(2,6-dimethylphenyl)-1-propene (IV) was prepared by reaction between allylbromide and 2,6-dimethylphenylmagnesium bromide (*cf.* for instance synthesis of *o*-allyltoluene [1]). To prepare 2-(2,6-dimethylphenyl)ethanol (V), 2,6-dimethylphenylmagnesium bromide was treated with ethylene oxide in dry tetrahydrofuran, the general directions by Ramsden *et al.*[2] for the preparation of phenethyl alcohol from chlorobenzene were followed. 2,6-Dimethylphenylacetonitrile * (VIII) was made *via* 2,6-dimethylbenzyl alcohol ** (VI) and the corresponding bromide (VII), VI being synthesized from 2,6-dimethylphenylmagnesium bromide and formaldehyde, as well as from 2,6-dimethylbenzoic acid and lithium aluminium hydride (see Chart 1 a). The reaction between 2,6-dimethylphenylmagnesium bromide and formaldehyde was carried out in dry diethyl ether and also in dry tetrahydrofuran, the latter medium giving a higher yield of VI (*cf.* experimental part).

Chart 1 a.



* Synthesized earlier by Raaen and Eastham [3] from 2,6-dimethylbenzyl chloride and sodium cyanide.

** Prepared earlier by Raaen and Eastham [3] by reducing ethyl 2,6-dimethylbenzoate with lithium aluminium hydride, and by Häring [4] from 2,6-dimethylbenzoyl chloride and the same reducing agent.

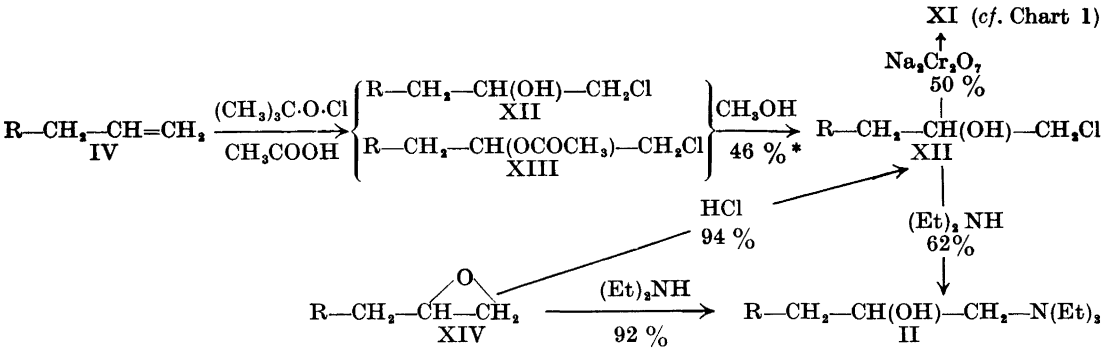
As outlined in Chart 1, the xylylacetic acid IX was made by three different methods, two of which were oxidations with potassium permanganate. Selective oxidation of an allyl compound with dilute aqueous potassium permanganate in a weak acetic acid medium to produce a substituted phenylacetic acid, *e.g.* 2-methoxy-*m*-tolylacetic acid, is described by Hill and Short [5]. Using this method for the synthesis of 2,6-dimethylphenylacetic acid (IX) from 3-(2,6-dimethylphenyl)-1-propene (IV), a 52 % yield was obtained (*cf.* Chart 1). No overoxidized contaminants, *e.g.* 2,6-dimethylbenzoic acid, could be found. Due to the risk of excess oxidation, permanganate is very seldom used for the oxidation of alcohols to the corresponding acids. In the opinion of the present investigators potassium permanganate is a rather suitable oxidizing agent for the conversion of alcohols into acids, provided that the experimental conditions are mild (low molar ratio, weak acidic medium, room temperature). Using potassium permanganate-acetic acid (concerning the conditions, see experimental part) to oxidize 2-(2,6-dimethylphenyl)ethanol (V) to 2,6-dimethylphenylacetic acid (IX), a rather good yield (60 %) was obtained.

The reduction of 1-diethylamino-3-(2,6-dimethylphenyl)-2-propanone (I) to 1-diethylamino-3-(2,6-dimethylphenyl)propane (III) with hydrazine hydrate [6] was carried out in a medium of triethylene glycol. Owing to the small difference in boiling point between III and triethylene glycol, III could not be purified by distillation (*cf.* Leonard and Gelfand [6]). However, chromatography of the mixture on an aluminium oxide column gave a good separation. — Surprisingly enough, the hydrochloride of I has a rather good solubility in *benzene*. In water the solubility is low (deprotonization of the rather strong onium acid).

Compound II was synthesized as demonstrated in Chart 2, which also shows other routes for the syntheses of I and III.

To Chart 2 the following additional details are given: Hanby and Rydon [7] describe a method for the preparation of styrene chlorohydrin from styrene and *tert*-butyl hypochlorite in a medium of acetic acid-water. In analogy

Chart 2.



* Calc. on IV.

with this method, it was attempted to prepare 1-chloro-3-(2,6-dimethylphenyl)-2-propanol (XII) from 3-(2,6-dimethylphenyl)-1-propene (IV) and *tert*-butyl hypochlorite. In this case the main product was found to be the desired chlorohydrin contaminated by the corresponding acetate (infrared and elementary analyses). The mixture of the two components was easily transformed into the alcohol XII by an ester-interchange procedure, using methanol and hydrochloric acid. The acetate XIII was isolated from the mixture by chromatography on an aluminium oxide column.

1-Chloro-3-(2,6-dimethylphenyl)-2-propanol (XII) was also prepared by coupling 2,6-dimethylphenyllithium with epichlorohydrin. The product first obtained was, however, not XII, but turned out to be 3-(2,6-dimethylphenyl)-1,2-epoxypropane (XIV). That this was the case was shown by infrared analysis (typical epoxy bands * at 1265 cm^{-1}, 920 cm^{-1}, 845 cm^{-1}, and 815 cm^{-1}; no alcohol band at 3600 cm^{-1}) and by elementary analysis. As far as we know, epichlorohydrin has not hitherto been found to couple with aryllithium compounds or arylmagnesium halides from the chlorine side, but always from the oxygen side (*cf.* for instance Elderfield[9], Gilman *et al.*[10], Fourneau and Tiffeneau [11] and Koelsch and McElvain [12]). In the opinion of the authors, the observed anomalous reaction has a simple explanation. Due to steric hindrance of the two methyl groups in *ortho*-position in 2,6-dimethylphenyllithium, the oxygen side of epichlorohydrin cannot approach the lithium atom. However, the chlorine side of the same molecule can easily contact the active center. This may clearly be demonstrated by using Stuart models. To obtain the desired 1-chloro-3-(2,6-dimethylphenyl)-2-propanol (XII), the epoxide (XIV) was cleaved by a new technique, using the calculated amount of dry *ether·HCl*, the reaction occurring spontaneously and quantitatively. By treating the same epoxide with diethylamine, compound II was prepared in a one-step reaction.

Compounds I, II, and III were tested for their local anesthetic action. Thus, the three compounds in the form of their bases were applied to the human tongue by rubbing. It was found that compound I, *i.e.* 1-diethylamino-3-(2,6-dimethylphenyl)-2-propanone, has a pronounced efficiency: on the tongue it gave roughly the same rapid onset and the same duration as Xylocaine ®. The two other compounds exhibited a very weak action, if any. Tests for sedative action were also made. These experiments were performed by subcutaneous injection in white mice, and the test solutions were prepared by dissolving the three compounds in 1,2-propylene glycol **-water (1:3) and hydrochloric acid, the pH-value being adjusted to 5.0. Compound I gave a distinct though not strong CNS depression, whereas II and III did not exhibit any appreciable effect. The sedative action of I was noticeable only at a relatively high dosage, *i.e.* sleep being induced by a quantity equal to approximately 75 % of the LD50. The LD50 values were determined by subcutaneous injections in white mice, the test solutions again contained propylene glycol. Thus the

* See for instance Bellamy [8].

** 25 % propylene glycol was used, since compound I — being a very weak base — cannot be dissolved in water to a desirable concentration without acidifying too much. II and III can easily be brought into aqueous solution without adding *excess* of acid, but for the sake of comparability, the test solutions of all three compounds were prepared using propylene glycol. In blank tests the 25 % propylene glycol solution did not show any pharmacological action.

LD50 values of compounds I, II, and III — expressed as g base per kg of body weight — were estimated to be 0.15, 0.40, and 0.025 respectively *. In special experiments (rabbits) the effect on blood pressure was studied. All three compounds gave a weak depressor action.

EXPERIMENTAL **

3-(2,6-Dimethylphenyl)-1-propene (IV). In a three-necked 500 ml flask equipped with a reflux condenser, a dropping funnel, and a sealed stirrer, 4.9 g (0.20 g atom) of magnesium [1] were reacted with 37.0 g (0.20 mole) of 2-bromo-1,3-dimethylbenzene in 120 ml of dry ether. When the reaction was complete, 24.2 g (0.20 mole) of allylbromide in 30 ml of dry ether were added. The mixture was treated with 50 g of crushed ice, and the ethereal layer was separated. The aqueous layer was extracted with two 50 ml portions of ether and the combined ethereal solutions were dried over sodium sulphate. After filtering, the ether was removed and 3-(2,6-dimethylphenyl)-1-propene (IV) distilled as a colourless liquid, b.p. 78°/12 mm, n_D^{25} 1.5181, yield 20.6 g (0.141 mole, 70 %). (Found: C 90.6; H 9.59. Calc. for $C_{11}H_{14}$ (146.2): C 90.4; H 9.65.)

2-(2,6-Dimethylphenyl)ethanol (V). In the same apparatus as described in the preparation of IV, 92.5 g (0.50 mole) of 2-bromo-1,3-dimethylbenzene [2] in 108 g of dry tetrahydrofuran were allowed to react with 12.2 g (0.50 g atom) of magnesium. When the spontaneous reaction had ceased, the mixture was refluxed for 15 min. The water condenser was now replaced by a glass coil surrounded by CO_2-ice in trichloroethylene. A well cooled solution of 22.0 g (0.50 mole) of ethylene oxide in 36 g of dry tetrahydrofuran was added during 5 min and the mixture was refluxed for 3 h. After cooling, the dark brownish oil was hydrolyzed with 46.5 ml of concentrated hydrochloric acid in 125 ml of water. The two layers were separated and the aqueous solution was extracted twice with 25 ml of toluene. The combined organic solutions were dried over sodium sulphate and, after filtering, the solvents were removed. The residue was distilled and 2-(2,6-dimethylphenyl) ethanol was collected as a colourless, rapidly crystallizing liquid, b.p. 95°/0.6 mm. Recrystallization from petroleum ether (b.p. 60–80°) gave colourless needles, m.p. 62.5–63.0°, yield 56.5 g (0.377 mole, 75 %). (Found: C 79.8; H 9.52. Calc. for $C_{10}H_{14}O$ (150.2): C 80.0; H 9.39.)

2,6-Dimethylbenzyl alcohol *** (VI). This compound was made by two different methods, *A* and *B*.

A. In a three-necked 500 ml flask equipped with a reflux condenser (cooled with CO_2-ice in trichloroethylene; *cf.* above), a sealed stirrer and a dropping funnel, 5.4 g (0.22 g atom) of magnesium were reacted with 37.0 g (0.20 mole) of 2-bromo-1,3-dimethylbenzene in 100 ml of dry tetrahydrofuran. The dropping funnel was then replaced by a wide glass tube, through which 9.0 g (0.30 mole) of gaseous formaldehyde [14] was slowly passed [15]. After 20 min, 50 g of ice and 215 ml of 2 M sulphuric acid were added. The tetrahydrofuran layer was separated off and the heavier layer extracted with four 50 ml portions of benzene. The combined organic layers were dried over sodium sulphate, and after removing the solvents, the solid residue was dried (m.p. of the crude product: 79–82°). Recrystallization from petroleum ether (b.p. 60–80°) gave colourless needles, m.p. 82.5–83.5° †, yield 20.9 g (0.154 mole, 77 %). In another experiment the reaction

* A concentration of 25 % propylene glycol in the aqueous solution of a tertiary amine of this type does not seem to affect the subcutaneous LD50 values in mice to any significant degree (Wiedling [13]).

** M.p.'s corrected; b.p.'s uncorrected. The determination of equivalent weights of synthesized bases was made by titrating them in glacial acetic acid with 0.1 N perchloric acid; BZL-Blue (CIBA) was used as an indicator. Chlorine in *hydrochlorides* was determined by potentiometric titration. *Infrared spectra* were recorded with the aid of a Beckman I R 5 Infrared Spectrophotometer.

*** See footnote, p. 1253.

† Recorded [3,4] m.p. 81–82°.

was carried out as described above, but in dry *ether*. The yield was found to be lower, *i.e.* 58 %.

B. In a three-necked 500 ml flask equipped with a reflux condenser, a sealed stirrer, and a dropping funnel, 7.5 g (0.050 mole) of 2,6-dimethylbenzoic acid in 60 ml of dry tetrahydrofuran were added to 2.4 g (0.063 mole) of lithium aluminium hydride [16] in 60 ml of dry tetrahydrofuran. When the spontaneous reaction had ceased, the mixture was refluxed for 4 h. After cooling, 1 ml of water was added and most of the tetrahydrofuran was removed by distillation under reduced pressure. To the residue, 100 ml of ether and 75 ml of 2 M sulphuric acid were added. The aqueous layer was extracted three times with 50 ml of ether. The combined ethereal solutions were washed with three 25 ml portions of 2 M sodium hydroxide. After removing the ether, the crystalline residue was dried. Recrystallization from petroleum ether (b.p. 40–60°) gave colourless needles of VI, m.p. 82.5–83.5° (recorded m.p., see above), yield 5.2 g (0.038 mole, 77 %).

In another experiment the reaction was carried out as described above, but in dry *ether* and under reflux for *ten* hours. In this case the yield was much lower, *i.e.* 49 %.

The infrared spectra of the products, obtained by methods *A* and *B*, were identical, and the mixed m.p. showed no depression.

2,6-Dimethylbenzyl bromide (VII). In a two-necked 500 ml flask equipped with a sealed stirrer and a reflux condenser, 20.4 g (0.15 mole) of 2,6-dimethylbenzyl alcohol (VI) and 175 ml of 48 % hydrobromic acid were stirred at a *bath* temperature of 100° for 4 h. The flask was then set aside in a refrigerator and the organic layer soon solidified. The aqueous layer was decanted and the crude bromide was dried on a porous plate and finally in a desiccator for 24 h. Recrystallization was made from petroleum ether (b.p. 60–80°) by cooling to −70° and the crystals thus obtained were sucked off at this temperature. Almost colourless crystals of m.p. 37.5–38.5° were obtained. Yield 27.8 g (0.140 mole, 93 %). (Found: C 54.3; H 5.65. Calc. for $C_9H_{11}Br$ (199.1): C 54.3; H 5.57.)

The compound is a strong lachrymator.

2,6-Dimethylphenylacetonitrile * (VIII). In a three-necked 250 ml flask equipped with a reflux condenser, a sealed stirrer, and a dropping funnel, 8.6 g (0.18 mole) of sodium cyanide were dissolved in 15 ml of water. After heating to 100° (bath temperature), 19.9 g (0.10 mole) of 2,6-dimethylbenzyl bromide (VII) in 20 ml of hot ethanol were slowly added and heating was continued for 3 h. The mixture was allowed to cool to 40° and was extracted with three 35 ml portions of benzene. The combined benzene solutions were washed three times with 25 ml of water and then dried over calcium chloride. The solvent was removed, and on distillation 2,6-dimethylphenylacetonitrile was collected as a colourless oil, b.p. 129–130°/12 mm, yield 12.2 g (0.084 mole, 84 %). After half an hour the oil crystallized. From ethanol-water (4:1) colourles sprisms of m.p.** 38.5–39.5° were obtained.

2,6-Dimethylphenylacetic acid (IX). This compound was made by three different methods, *A*, *B*, and *C*.

A ***. Under vigorous stirring, 4.3 g (0.030 mole) of 3-(2,6-dimethylphenyl)-1-propene (IV) were emulsified in 400 ml of ice-water and 13.0 g (0.22 mole) of glacial acetic acid. Under continued stirring and during 1 h, 380 ml of a 5 % solution of potassium permanganate (0.12 mole) were added, the reaction temperature being kept at 0°. The mixture was made alkaline with dilute sodium hydroxide and then filtered. The filtrate was concentrated under reduced pressure to 75 ml and then acidified with hydrochloric acid. The precipitate was filtered off, washed with 5 ml of cold water and dried. M.p. of the crude product: 118–122°. Recrystallization from water gave colourless leaflets, m.p. 129–130°. Yield 2.6 g (0.016 mole, 52 %). (Found: C 72.7; H 7.35. Calc. for $C_{10}H_{12}O_2$ (164.2): C 73.1; H 7.37.)

B. By the same technique as described under *A*, 4.5 g (0.030 mole) of 2-(2,6-dimethylphenyl)ethanol (V) was oxidized by 190 ml of a 5 % solution of potassium permanganate (0.060 mole). Since the reaction proved to be slow at 0° (*cf.* previous description *A*) the temperature was raised to 30°. The crystals obtained melted at 119–124°. From water,

* See footnote p. 1253.

** Recorded [3] m.p. 39.5–40.5°.

*** The general directions for the preparation of 2-methoxy-*m*-tolylacetic acid [5] were followed.

colourless leaflets were obtained; m.p. 129—130°, in agreement with the value found for IX (see previous description *A*). Yield 2.9 g (0.018 mole, 60 %).

C. In a three-necked 250 ml flask equipped with a reflux condenser, a sealed stirrer and a dropping funnel, a mixture of 3.6 g (0.025 mole) of 2,6-dimethylphenylacetonitrile (VIII), 30 ml of water, and 25 ml of concentrated sulphuric acid was refluxed for 6 h (bath temperature 120°). The reaction mixture was then poured into 100 ml of ice-water. The crystals were filtered off and washed twice with 5 ml of cold water. From water, colourless leaflets were obtained; m.p. 129—130°, in accordance with the value found for IX (see previous description *A*). Yield 3.6 g (0.022 mole, 87 %).

The identity of the three products was further demonstrated by taking mixed m.p.'s and infrared spectra.

2,6-Dimethylphenylacetyl chloride (X). A mixture of 9.9 g (0.060 mole) of 2,6-dimethylphenylacetic acid (IX) and 14.3 g (0.12 mole) of thionyl chloride was heated at 40° (bath temperature) for 2 h. The excess of thionyl chloride was removed and X was distilled as a colourless liquid, b.p. 124°/17 mm, n_D^{25} 1.5345, yield 8.9 g (0.049 mole, 81 %). Found: C 66.1; H 6.00. Calc. for $C_{10}H_{11}ClO$ (182.7): C 65.8; H 6.07.)

1-Chloro-3-(2,6-dimethylphenyl)-2-propanone (XI). This compound was prepared by two different methods, *A* and *B*.

A. In a three-necked 250 ml flask equipped with a dropping funnel, a sealed stirrer, and a reflux condenser, 4.6 g (0.025 mole) of 2,6-dimethylphenylacetyl chloride (X) in 5 ml of dry ether were added to 0.050 mole of diazomethane * in 125 ml of dry ether **. After 2 h the flask was surrounded by ice-water and to the cooled solution dry hydrogen chloride was introduced during 30 min. 50 ml of water were added and the two layers were separated. The aqueous layer was extracted twice with 30 ml of ether. The combined ethereal solutions were washed twice with 25 ml of a 5 % solution of sodium carbonate and then dried over calcium sulphate. The solvent was removed and the crystalline residue dried. M.p. of the crude product: 38—40°. After recrystallization from petroleum ether (b.p. 40—60°) colourless needles were isolated, m.p. 43—44°, yield 4.2 g (0.021 mole, 86 %). (Found: C 67.3; H 6.79. Calc. for $C_{11}H_{13}ClO$ (196.7): C 67.2; H 6.66.)

B. A mixture of 9.9 g (0.050 mole) of 1-chloro-3-(2,6-dimethylphenyl)-2-propanol (XII),*** 8.5 g (0.029 mole) of sodium dichromate, and 5 ml of a 50 % acetone-water solution(v/v) was immersed in cold water and stirred into an emulsion †. During 7 h, 5.3 ml of concentrated sulphuric acid in 2.5 ml of water were added. The reaction temperature was kept between 20° and 25° during the entire reaction. Stirring was continued for a further 16 h. 15 ml of water were then added and the mixture was extracted twice with 15 ml of ether. The combined ethereal solutions were dried over sodium sulphate. After filtering, the solvent was removed and from the residue a colourless, rapidly crystallizing oil was distilled, b.p. 95—97°/0.1 mm. After recrystallization from petroleum ether (b.p. 40—60°) colourless needles were obtained. M.p. 44—45°, in agreement with the value found for XI (see previous description *A*). The identity of the two products was further demonstrated by taking infrared spectra.

1-Diethylamino-3-(2,6-dimethylphenyl)-2-propanone (I). A mixture of 3.9 g (0.020 mole) of 1-chloro-3-(2,6-dimethylphenyl)-2-propanone (XI) and 3.8 g (0.052 mole) of diethylamine in 10 ml of dry benzene was refluxed for 5 h. After cooling, diethylammonium chloride separated and was filtered off. The filtrate was extracted twice with 7 ml of 3 M hydrochloric acid and the combined extracts were then washed with two 5 ml portions of ether. The aqueous solution was made alkaline with concentrated ammonia and the liberated base taken up in 5 ml of ether. From the dried ethereal solution (potassium carbonate) the solvent was removed, and by distillation of the residue a colourless oil was obtained, b.p. 120°/1.0 mm, yield 3.4 g (0.015 mole, 73 %). After some time the oil solidified to a crystalline mass. Recrystallization was made from di-isopropyl ether by cooling to −25° and the crystals thus obtained were sucked off at this temperature; colourless prisms of m.p. 34—36°. (Found: Equiv. wt. 233. Calc. for $C_{15}H_{23}NO$: 233.4.)

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* As obtained from 10 ml of nitrosomethylurethan (see McPhee and Klingsberg [17]).

** The directions given for the preparation of 1-chloro-3-phenyl-2-propanone [17] were followed.

*** For the preparation of XII, see below.

† The directions given for the preparation of 1-chloro-4-phenyl-2-butanone [18] were followed.

Hydrochloride. The base was dissolved in dry ether and the required amount of dry ether·HCl was added. The microcrystalline precipitate formed (m.p. 135—136°) was then recrystallized from benzene. Colourless needles of m.p. 135—136° were obtained. (Found: Cl 13.0. Calc. for $C_{15}H_{24}ClNO$ (269.8): Cl 13.1.)

1-Diethylamino-3-(2,6-dimethylphenyl)propane (III). A mixture of 6.5 g (0.028 mole) of 1-diethylamino-3-(2,6-dimethylphenyl)-2-propanone (I), 5.0 ml (0.085 mole) of 85 % hydrazine hydrate, 5.6 g (0.10 mole) of potassium hydroxide and 15 ml of triethylene glycol was refluxed at 115° (bath temperature) for 2 h *. The condenser was then set for downward distillation and the temperature inside the reaction flask was raised to 200°, where it was maintained until distillation ceased. The distillate and the water-diluted residue were each extracted four times with 5 ml of ether, each aqueous layer then saturated with sodium carbonate and extracted again in the same way. The combined ethereal extracts were dried over magnesium sulphate, the ether removed and the residue distilled as a colourless oil, b.p. 100—105°/2 mm. This oil was found to be (infrared spectrum) a mixture of III and triethylene glycol (*cf.* theor. part). The obtained mixture was dissolved in 5 ml of dry ether and this solution was then poured on an aluminium oxide ** column (1.2 by 18 cm). The column was washed with 25 ml of dry ether. Yellowish impurities were retained near the top of the column, the entire effluent being colourless. The purified ethereal solution was freed from the solvent, and the residue was then distilled *in vacuo*. III was collected as a colourless oil, b.p. 74—75°/1 mm, n_D^{25} 1.5050, yield 3.2 g (0.015 mole, 52 %). (Found: Equiv.wt. 221. Calc. for $C_{15}H_{25}N$: 219.4.)

Hydrochloride. Precipitated in dry ether with dry ether·HCl; *cf.* the preparation of the hydrochloride of I. From di-isopropyl ether — isopropyl alcohol (10:1, v/v) colourless prisms of m.p. 126—127° were obtained. (Found: Cl 13.8. Calc. for $C_{15}H_{26}ClN$ (255.8): Cl 13.8.)

3-(2,6-Dimethylphenyl)-1,2-epoxypropane *** (XIV). In a four-necked 250 ml flask equipped with a reflux condenser, a dropping funnel, a sealed stirrer, and an argon inlet tube, 1.5 g (0.21 g atom) of lithium sand [19] in 25 ml of dry ether were placed. To this mixture 18.5 g (0.10 mole) of 2-bromo-1,3-dimethylbenzene in 50 ml of dry ether were slowly added during one hour. When the reaction was complete, a sample of the ethereal solution was titrated with hydrochloric acid (*cf.* Jones and Gilman [20]). The yield of 2,6-dimethylphenyllithium by this titration was found to be 99 %. A three-necked flask with an argon inlet tube, a sealed stirrer, and a dropping funnel, was charged with 9.3 g (0.10 mole) of epichlorohydrin in 15 ml of dry ether. The solution was cooled to —78° in a CO_2-ice-trichloroethylene-bath and 0.10 mole of 2,6-dimethylphenyllithium (*cf.* above) in 75 ml of dry ether was added during 30 min. The mixture was stirred at —78° (bath temperature) for 1.5 h and was then kept overnight at the same temperature. The bath was then allowed to warm slowly to 0° during 5 h. At that time test for organolithium compound [21] was negative. To the mixture 20 ml of 3 M sulphuric acid and 5 g of crushed ice were added. The ethereal layer was separated and washed twice with 75 ml of water. After drying over sodium sulphate, the ether was removed by distillation. The product was distilled at 83°/0.05 mm, n_D^{25} 1.5330, yield 6.3 g (0.039 mole, 39 %). (Found: C 81.0; H 8.92. Calc. for $C_{11}H_{14}O$ (162.2): C 81.4; H 8.70.)

Infrared spectrum of XIV, dissolved in carbon disulphide, showed bands typical for the epoxy structure at 1265 cm^{-1}, 920 cm^{-1}, 845 cm^{-1} and 815 cm^{-1} (*cf.*, *e.g.*, Bellamy [8]). No band characteristic for the alcohol group (3600 cm^{-1}) could be found in the spectrum of XIV (*cf.* footnote on p. 1259).

1-Chloro-3-(2,6-dimethylphenyl)-2-propanol (XII). This compound was made by two different methods, *A* and *B*.

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* The method described by Leonard and Gelfand [6] for the preparation of 1-phenyl-3-(N-piperidyl)propane was followed.

** "Woelm, basisch, Akt. Stufe I".

*** In the synthesis of 1-chloro-3-phenyl-2-propanol described by Gilman *et al.*[10] epichlorohydrin couples, as expected,[9,11,12] with phenyllithium from the oxygen side. The method of these authors was followed by reacting 2,6-dimethylphenyllithium with epichlorohydrin, with the intention of obtaining 1-chloro-3-(2,6-dimethylphenyl)-2-propanol (XII). Surprisingly enough, the resulting compound was not XII but 3-(2,6-dimethylphenyl)-1,2-epoxypropane (XIV), *i.e.* in this case the epichlorohydrin coupled from its chlorine side (*cf.* p. 1255).

A. 8.1 g (0.050 mole) of 3-(2,6-dimethylphenyl)-1,2-epoxypropane (XIV) were treated with 23 ml of 2.4 M ether·HCl (0.055 mole of HCl). The ether was removed and the residual colourless crystals were washed with 10 ml of petroleum ether (b.p. 40 – 60°) and then dried. M.p. of the crude product: 43 – 44°. After recrystallization from petroleum ether (b.p. 40 – 60°), colourless rhombohedral crystals of m.p. 47 – 48° were obtained. Yield 9.3 g (0.047 mole, 94 %). (Found: C 66.5; H 7.61. Calc. for $C_{11}H_{15}ClO$ (198.7): C 66.5; H 7.61.)

B. A mixture of 15.0 g (0.10 mole) of 3-(2,6-dimethylphenyl)-1-propene (IV), 100 ml of water, and 10 ml of glacial acetic acid was stirred into an emulsion (*cf.* p. 1254). Under continued stirring, 11.4 g of *tert*-butyl hypochlorite of 95 % purity * (0.10 mole) were added at such a rate that the temperature remained below 25° (external cooling by cold water). After the addition was complete, the mixture was stirred for a further 2 h. The two layers were then separated. The aqueous layer was extracted twice with 20 ml of ether and the combined ethereal extracts were dried over sodium sulphate. The residue obtained after evaporation of the filtered ethereal solution, was distilled as a colourless oil, b.p. 110 – 115°/0.5 mm, yield 10.4 g. The substance proved to be a mixture,** containing the expected chlorohydrin (XII) contaminated with the corresponding acetate, *viz.* 1-chloro-3-(2,6-dimethylphenyl)-2-propyl acetate (XIII). In order to transform the contaminant, *i.e.* the acetate XIII, into the alcohol XII, the mixture was refluxed with 5 ml of concentrated hydrochloric acid and 250 ml methanol for 2 h. Methyl acetate, formed by transesterification, and methanol were then distilled *slowly* until 25 ml remained. Another portion of 250 ml methanol was then added and the procedure repeated. To the brown, oily residue, 10 ml of water were added and the mixture was neutralized with 2 M sodium hydroxide. After extracting twice with 50 ml of ether, the combined ethereal solutions were dried over sodium sulphate. After filtering, the ether was removed, giving a residue of colourless crystals. They were washed with petroleum ether (b.p. 40 – 60°) and then dried, m.p. 43 – 46°. From petroleum ether (b.p. 40 – 60°) colourless rhombohedral crystals were obtained; m.p. 46 – 47°, in agreement with the value found for XII (see previous description *A*), yield 9.2 g (0.046 mole, 46 %). The identity of the two products was further demonstrated by infrared spectra.

1-Chloro-3-(2,6-dimethylphenyl)-2-propyl acetate (XIII). 4.8 g of the mixture consisting of XII and XIII (*cf.* the preparation of XII, method *B*) were dissolved in 10 ml of benzene. This solution was poured on an aluminium oxide *** column (2.2 by 30 cm). The chromatogram was developed with the same solvent. The 30 – 55 ml fraction was collected and the benzene then removed by distillation. The residue was distilled as a colourless oil, b.p. 108 – 110°/2 mm, n_D^{25} 1.5161, yield 0.40 g (0.0017 mole). (Found: C 65.0; H 7.18. Calc. for $C_{13}H_{17}ClO_2$ (240.7): C 64.9; H 7.12.)

1-Diethylamino-3-(2,6-dimethylphenyl)-2-propanol (II). This compound was made by two different methods, *A* and *B*.

A. A mixture of 2.0 g (0.012 mole) of 3-(2,6-dimethylphenyl)-1,2-epoxypropane (XIV) and 5.0 g (0.068 mole) of diethylamine was heated in an autoclave at 120° for 10 h. After evaporation of the excess of diethylamine, a crystalline mass was collected. Recrystallization from ethanol-water (1:1, v/v) gave colourless needles of m.p. 59 – 60°, yield 2.7 g (0.011 mole, 92 %). (Found: Equiv. wt. 236. Calc. for $C_{15}H_{25}NO$: 235.4.)

B. The compound was also prepared from 8.0 g (0.040 mole) of 1-chloro-3-(2,6-dimethylphenyl)-2-propanol (XII) and 7.6 g (0.10 mole) of diethylamine using the same technique as described in the preparation of I. — After evaporation of the solvent (ether; *cf.* preparation of I) a crystalline mass was obtained. This was recrystallized from ethanol-water (1:1, v/v); m.p. 60 – 61°, in agreement with the value found for II, when prepared according to method *A* (*cf.* above). Yield 5.9 g (0.025 mole, 62 %). The identity of the two products was further demonstrated by infrared spectra.

Methiodide †. 0.4 g (0.0017 mole) of the base II in 1 ml of dry acetonitrile was treated with 0.28 g (0.0020 mole) of methyl iodide. After 12 h the crop of colourless crystals was

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* See Westwater and Audrieth [22].

** Analysis by means of infrared spectrum (*cf.* p. 1255).

*** "Woelm, neutral, Akt. Stufe I".

† Attempts were made to prepare other salts, *viz.* the hydrochloride, the perchlorate, the methanesulphonate, and the picrate. However, no crystalline products could be obtained.

collected. From acetonitrile, colourless needles of m.p. 152—153° were obtained. (Found: C 51.0; H 7.48. Calc. for $C_{16}H_{28}INO$ (377.3): C 50.9; H 7.48.)

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