296. *Syntheses of Neurotropic and Musculotropic Stimulators and Inhibitors. Part III.* Derivatives of Unsaturated ω-Betaines.*

By F. Bergel, A. Cohen, and N. C. Hindley.

The Doebner–Knoevenagel reaction with aldehydic quaternary ammonium salts and malonic acid provides a synthesis of unsaturated ω-betaines, including the known trimethyl-(3-carboxyallyl)ammonium chloride (II; R = H, X = Cl) or crotonobetaine hydrochloride. The latter is esterified with the appropriate alcoholic hydrogen chloride, and a new procedure, through the acid chloride obtained by thionyl chloride, is described, yielding the new benzyl, *n*-amyl, and *n*-octyl esters, which represent water-soluble derivatives of these alcohols. The acid chloride also yields the amide and carbethoxymethylamide. Trimethyl-(3-carbethoxy-2-ethoxyallyl)ammonium bromide has also been prepared.

Reference is made to pharmacological experiments with some of these compounds.

γ-Crotonobetaine (I) has been isolated in small quantities from beef muscle by Linneweh (*Z. physiol. Chem.*, 1928, **175**, 91) who synthesised its hydrochloride (II; R = H, X = Cl) from ethyl γ-chlorocrotonate and trimethylamine (*ibid.*, 1928, **176**, 217), and found that it resembled γ-butyrobetaine in pharmacological effects, which were " curare-like " and weakly parasympathomimetic (*ibid.*, 1929, **181**, 42). According to Strack and Foersterling (*Ber.*, 1938, **71**, 1143; 1943, **76**, 14; *Z. physiol. Chem.*, 1938, **257**, 1; 1942, **277**, 74), who prepared the unsaturated betaine from L-carnitine as described by Engeland (*Ber.*, 1921, **54**, 2208), the parasympathomimetic activity was considerably increased by esterification. Thus, the methyl ester (II; R = Me, X = Cl) showed muscarinic and nicotinic effects which were about one-tenth of those of acetylcholine when tested on muscle preparations. Such relatively high physiological activity of a compound differing biochemically from the neuro-hormone of the parasympathetic nervous system in its resistance to cholinesterase, and, chemically, in that the quaternary ammonium group resides in the acid half of the ester molecule, prompted us to re-examine the synthesis and pharmacological properties of γ-crotonobetaine and related substances some time ago (1942, B.P. 546,596, 546,613, 546,614, and 547,057).

By a Doebner–Knoevenagel reaction with malonic acid and formyltetramethylammonium chloride (III) obtained from trimethylamine and bromoacetal (cf. Berlinerblau, *Ber.*, 1884, **17**, 1139), trimethyl-(3-carboxyallyl)ammonium chloride (γ-crotonobetaine hydrochloride) (II; R = H, X = Cl) has been synthesised. It showed m. p.s ranging from 180° to 199° but, after careful recrystallisation and drying, a deliquescent salt was obtained which decomposed at 200—203° (Linneweh, *loc. cit.*, quotes 203—205°). As the m. p.s of the picrate and chloroplatinate, and of the salt of the corresponding methyl ester (II; R = Me), discussed below, agreed with those given in the literature (Linneweh, *loc. cit.*; Strack and Foersterling, *Ber.*, 1938, *loc. cit.*), there can be little doubt that our compounds were identical with those of the German authors. Observations on the chloroaurate of crotonobetaine which differ somewhat from those in the literature are recorded in the Experimental section. The assignment of αβ- rather than βγ-unsaturation to the products of the present synthesis is based on analogy to a number of examples of the Doebner–Knoevenagel reaction (cf. " Organic Reactions," Vol. I, p. 226). Although it is realised that these comparisons are drawn between products from non-basic and basic aldehydes, the further assumption of the stable crotonic acid configuration is in

* The following papers are to be regarded as Parts I and II, respectively, in this series: *J.*, 1943, 48, 49.

line with the findings of Scheibler and Magasanik (*Ber.*, 1915, **48**, 1810) and von Auwers (*Annalen*, 1923, **432**, 46) that the analogous condensation of acetaldehyde and malonic acid in pyridine leads to crotonic acid and not *iso*crotonic acid.

$$\underset{\text{(I.)}}{Me_3N^+\cdot CH_2\cdot CH{:}CH\cdot CO_2^-} \qquad \underset{\text{(II.)}}{Me_3N\cdot CH_2\cdot CH{:}CH\cdot CO_2R} \longleftarrow \underset{\text{(III.)}}{Me_3N\cdot CH_2\cdot CHO} + CH_2(CO_2H)_2$$

This method of synthesis has been extended to other aldehydic quaternary ammonium salts. Thus, formylmethyltriethylammonium chloride, obtained by condensation of triethylamine and bromoacetal followed by acid hydrolysis, yielded, with malonic acid, a deliquescent quaternary chloride from which triethyl-(3-carboxyallyl)ammonium reineckate was obtained.

Similarly, trimethyl-(4-carboxybut-3-enyl)ammonium chloride has been synthesised from trimethyl-(2-formylethyl)ammonium chloride which was prepared in a manner similar to that reported by Voet (*Bull. Soc. chim.*, 1929, [iv], **45**, 1016).

In view of the above-mentioned physiological importance of esters of type (II), their preparation was further studied. The methyl ester (II; R = Me), prepared with methanolic hydrogen chloride according to Strack and Foersterling (*Ber.*, 1938, *loc. cit.*), was isolated as reineckate [X = $Cr(CNS)_4(NH_3)_2$], chloride (X = Cl), and sulphate (X = $\frac{1}{2}SO_4$). In an alternative procedure (II; R = H, X = Cl) was treated with thionyl chloride and the resulting crude acid chloride, which could not be readily purified, yielded esters on treatment with alcohols. The methyl ester prepared in this way for the first time yielded the same reineckate and sulphate as were obtained by the methanolic hydrogen chloride route, and the benzyl ester similarly prepared gave trimethyl-(3-carbobenzyloxyallyl)ammonium reineckate, chloride, and iodide [II; R = CH_2Ph, X = $Cr(CNS)_4(NH_3)_2$, Cl, and I, respectively]. That the same ester was obtained by esterification of (II; R = H, X = Cl) with benzyl alcohol and hydrogen chloride was shown by the identity of the characteristic reineckates.

Higher alcohols also react readily with the crude acid chloride product from thionyl chloride, yielding water-soluble esters, analogous to those obtained by Plattner and Geiger (*Helv. Chim. Acta*, 1945, **28**, 1362) from betainyl dichloride.

In this manner the *n*-amyl ester reineckate and sulphate [II; R = *n*-C_5H_{11}, X = $Cr(CNS)_4(NH_3)_2$ and $\frac{1}{2}SO_4$, respectively], and the *n*-octyl ester reineckate were obtained. Conversion of the latter into the corresponding sulphate did not yield a crystalline product; in aqueous solution it behaved as an " inverted " soap, showing marked lowering of surface tension.

Treatment of the crude acid chloride or the methyl ester (II; R = Me, X = Cl), prepared by either method, yielded with ammonia, the corresponding amide which was isolated in the form of reineckate, chloride, and sulphate. The reaction of the acid chloride with ethyl aminoacetate led to the carbethoxymethylamide (II; $NH\cdot CH_2\cdot CO_2Et$ for OR) isolated in the form of its reineckate and deliquescent sulphate. It was of interest at the time to examine this compound for oxytocic activity but practically no effect on the guinea-pig uterus was found. Gulland, Partridge, and Randall (*J.*, 1940, 419) had prepared choline esters of amino-acids and peptides as possible simple analogues of the oxytocic principle of the posterior lobe of the pituitary gland.

Since choline ethers (Dale, *J. Pharm. Exp. Ther.*, 1914, **6**, 147) and trimethyl-(2-methoxyallyl)ammonium bromide (" Esmodil ") (Hecht, *Klin. Woch.*, 1935, **14**, 957) are known to possess strong muscarinic activity, it appeared desirable to synthesise a compound incorporating the alkoxy-group of these two types in a crotonic acid betaine ester.

Accordingly, ethyl γ-bromo-β-ethoxycrotonate (IV), prepared from ethyl β-ethoxycrotonate and *N*-bromoacetamide (Wohl and Jaschinowski, *Ber.*, 1921, **54**, 476), was treated with trimethylamine, yielding trimethyl-(3-carbethoxy-2-ethoxyallyl)ammonium bromide (V).

$$\underset{\text{(IV.)}}{Br\cdot CH_2\cdot C(OEt){:}CH\cdot CO_2Et} + Me_3N \longrightarrow \underset{\text{(V.)}}{Me_3N\cdot CH_2\cdot C(OEt){:}CH\cdot CO_2Et}$$

Preliminary pharmacological tests performed partly by courtesy of the Pharmacological Department of Messrs. F. Hoffmann–La Roche, Basle, and partly by Mr. M. W. Parkes of these laboratories, confirmed the recorded reports as to the parasympathomimetic action of the methyl ester (II; R = Me). The ethoxy-derivative (V), however, showed only weak activity, so that, at least as far as concerns ethoxy- and carbethoxy-groups, the simultaneous presence of the ether and ester groups in the allyl chain tends to abolish acetylcholine-like effect.

A more detailed pharmacological study of the methyl and benzyl esters (II; R = Me and CH_2Ph respectively) has now been reported by Burgen and Hobbiger (*Brit. J. Pharm.*, 1949, **4**, 229).

Experimental.

(M. p.s are uncorrected.)

Formyltetramethylammonium Chloride (III).—*Trimethyl-2 : 2-diethoxyethylammonium bromide* was first prepared by the following convenient procedure as an alternative to that of Fischer (*Ber.*, 1893, **26**, 464) who prepared the iodide by methylation of aminoacetal. A mixture of bromoacetal (25 g.), anhydrous trimethylamine (14 g.), and benzene (25 c.c.) was heated in a sealed tube at 90—100° for 48 hours (cf. Berlinerblau, *Ber.*, 1884, **17**, 1139) After cooling, the crystalline product was collected, washed with dry benzene, and dried (31 g., 95·5%). After crystallisation from alcohol–ether it had m. p. 150—152° (Found : Br, 31·3. $C_9H_{22}O_2NBr$ requires Br, 31·2%). A solution of this bromide (58·7 g.) in water (200 c.c.) was shaken for 30 minutes with moist silver oxide freshly prepared from silver nitrate (43 g.). To the halogen-free filtrate and aqueous washings (total, 325 c.c.) concentrated hydrochloric acid (60 c.c.) was added and the whole boiled under reflux for 20 minutes in a nitrogen atmosphere and evaporated to dryness under reduced pressure. The crystalline residue of *formyltetramethylammonium chloride hydrate* (32·55 g.), washed with dry acetone and dried *in vacuo*, had m. p. 123—124° (Found : Cl, 22·8. $C_5H_{12}ONCl,H_2O$ requires Cl, 22·8%). Fischer (*loc. cit.*) and Berlinerblau (*loc. cit.*) did not give analytical data for their compound but characterised it as chloroplatinate.

Trimethyl(3-carboxyallyl)ammonium Chloride (II; R = H, X = Cl).—A mixture of the above aldehydic salt (15·7 g), malonic acid (15 g.), and dry pyridine (70 c.c.) was heated with stirring on a boiling water-bath for 2 hours. Malonic acid (3 g.) was again added and heating continued for a further hour. Pyridine was removed under reduced pressure and the residue dried by azeotropic distillation with benzene. The product was digested with ethyl acetate, and the crystalline mass dissolved in absolute ethanol (48 c.c.). On cooling to −5° a first crop (8·9 g.; m. p. 190—195°) was obtained and from the mother-liquor a further 2·5 g. (m. p. 190—195°) separated on storage. Recrystallisation from ethanol yielded material which, after careful drying, had m. p. 200—203° (decomp.) (Found : Cl, 19·55. Calc. for $C_7H_{17}O_2NCl$: Cl, 19·8%) ; the picrate had m. p. 187°, and the chloroplatinate m. p. 223—224° (decomp.). Linneweh (*loc. cit.*) gives 203—205°, 187—189°, and 221—222° (decomp.), respectively.

In some experiments, further crops of the crotonobetaine hydrochloride melted as low as *ca.* 180°. The chloroaurate of this material, however, obtained in nearly theoretical yield had m. p. 202—203° (decomp.) (Found : C, 17·8; H, 2·9; N, 2·8; Au, 40·2. Calc. for $C_7H_{14}O_2N,AuCl_4$: C, 17·4; H, 2·9; N, 2·9; Au, 40·8), whereas the chloroaurate of the first crop, obtained in equal yield, had m. p. 200—201° (decomp.) (Found : C, 17·6; H, 2·6; N, 2·95; Au, 40·3). The mixed m. p. was 204—205°. Engeland (*loc. cit.*) gives 190—195°, and Linneweh (*loc. cit.*) 215—217° for this m. p.

Triethyl-(3-carboxyallyl)ammonium Reineckate.—(Formylmethyl)triethylammonium chloride (1·5 g.), prepared according to Stoermer and Prall (*Ber.*, 1897, **30**, 1504), was heated with malonic acid (1 g.) and dry pyridine (10 c.c.) on a boiling water-bath. Evolution of carbon dioxide was brisk, and heating was continued for 1 hour, with occasional shaking. After removal of the pyridine under reduced pressure the residue was dried over phosphoric oxide, dissolved in absolute ethanol (4 c.c.), and treated with dry ether (8 c.c.). The chloride was thus precipitated as an uncrystallisable oil. It readily yielded a crystalline *reineckate*, m. p. 154—155° (from aqueous acetone) (Found : C, 33·2; H, 5·8; N, 19·0. $C_{14}H_{26}O_2N_7S_4Cr$ requires C, 33·4; H, 5·1; N, 19·5%).

Trimethyl-(4-carboxybut-3-enyl)ammonium Chloride.—3-Chloropropaldehyde diethyl acetal (5 g.) was heated with trimethylamine (3·9 g.) in ethanol (12·5 c.c.) for 15 hours at 100° in a sealed tube (cf. Voet, *Bull. Soc. chim.*, 1929, [iv], **45**, 1016). The solution was concentrated to a small volume under reduced pressure and treated with dry ether which precipitated a light-brown deliquescent solid (3 g.). A solution of this in water (10 c.c.) and concentrated hydrochloric acid (10 c.c.) was left overnight at room temperature in a nitrogen atmosphere to hydrolyse the acetal. Evaporation to dryness *in vacuo* yielded a residue of 2 g. This was heated with malonic acid (2 g.) and dry pyridine (15 c.c.) on a boiling water bath for 3 hours. The mixture was then evaporated under reduced pressure and dried *in vacuo* over phosphoric oxide. The residue was dissolved in a small amount of ethanol and precipitated with dry ether, yielding an oily *chloride* which was converted by digestion with ether into a light-brown deliquescent solid, further purification of which was effected by precipitation from alcoholic solution by dry ether (Found : Cl, 18·3. $C_8H_{16}O_2NCl$ requires Cl, 18·3%). It yielded, by the usual treatment, a reineckate of m. p. 204—207°.

Trimethyl-(3-carbomethoxyallyl)ammonium Salts (II; R = Me).—(*a*) Crotonobetaine hydrochloride (5 g.) was esterified with methanolic hydrogen chloride as described by Strack and Foersterling (*loc. cit.*). It was directly converted into the reineckate (11·1 g.) which formed purple-pink needles, m. p. 159—163°, after recrystallisation from aqueous acetone (Found : C, 30·2; H, 4·5; N, 20·15. Calc. for $C_{12}H_{22}O_2N_7S_4Cr$: C, 30·3; H, 4·6; N, 20·6%).

A solution of the reineckate in acetone–water (1 : 4) was treated with the calculated amount of silver sulphate in aqueous solution, filtered from silver reineckate, and treated with barium chloride solution (cf. Strack and Foersterling, *loc. cit.*). After removal of barium sulphate and complete evaporation under reduced pressure and at low temperature, the residue was crystallised from acetone–methanol, yielding trimethyl-(3-carbomethoxyallyl)ammonium chloride, a deliquescent solid, m. p. 171—174° (decomp.) (Found : Cl, 18·3. Calc. for $C_8H_{16}O_2NCl$: Cl, 18·3%).

A solution of the reineckate (0·447 g.) in acetone–water (3·5 c.c.; 4 : 1) was treated with a cold aqueous solution of silver sulphate (0·1468 g.; 38 c.c.). The silver reineckate was filtered off and washed with aqueous acetone, and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in methanol, filtered clear, and concentrated to a small volume. Addition of acetone yielded the very deliquescent *trimethyl-(3-carbethoxyallyl)ammonium sulphate*, m. p. 164—165° (decomp.) when anhydrous [Found : C, 46·8; H, 7·4; N, 7·0. $(C_8H_{16}O_2N)_2SO_4$ requires C, 46·5; H, 7·8; N, 6·8%].

(*b*) Crotonobetaine hydrochloride (1 g.) was gently warmed with thionyl chloride (4 c.c.) for 10 minutes on the water-bath. Excess of thionyl chloride was removed at low temperature under

reduced pressure. The residue was triturated with dry ether, but further attempts at purification were unsuccessful. The product (1·1 g.), consisting of the acid chloride, was mixed with absolute methanol (4 c.c.), and the resulting solution boiled for 10 minutes. Methanol (1 c.c.) was again added and boiling continued for a further 5 minutes. After dilution of the cooled solution with ice-water and extraction with ether, the aqueous solution was made slightly alkaline with dilute aqueous ammonia and treated with saturated aqueous ammonium reineckate solution. The precipitated purple-pink reineckate was collected, dried (2·4 g.), and recrystallised by cautious addition of water to a clarified warm acetone solution. It had m. p. 159—161° and was identical with the reineckate described above under (*a*) (mixed m. p. 161—163°) (Found: C, 30·9; H, 4·5; N, 20·4; Cr, 10·2. Calc. for $C_{12}H_{22}O_2N_7S_4Cr$: C, 30·3; H, 4·6; N, 20·6; Cr, 10·9%).

The reineckate was converted into the sulphate as described above, and this material, m. p. 165°, was identical with the sulphate obtained from the methanolic hydrogen chloride esterification (mixed m. p. 164—165°) [Found: C, 46·3; H, 7·4; N, 6·8. Calc. for $(C_8H_{16}O_2N)_2SO_4$: C, 46·5; H, 7·8; N, 6·8%].

Trimethyl-(3-carbobenzyloxyallyl)ammonium Salts (II; R = CH_2Ph).—*Reineckate* [X = $Cr(CNS)_4(NH_3)_2$]. Crotonobetaine hydrochloride (1·42 g.) was converted into the crude acid chloride as already described and this was heated with benzyl alcohol (6 c.c.) for 10 minutes on a boiling water-bath. The dark liquid was cooled and diluted with water, and excess of benzyl alcohol removed by extraction with ether. The aqueous solution, made alkaline to litmus with dilute aqueous ammonia, was treated with a clear solution of ammonium reineckate. The precipitated *reineckate* was collected and dried (4·12 g.) and recrystallised from acetone–water, forming pink needles, m. p. 166—169°. This was identical with the reineckate of the benzyl ester prepared in the following manner (no depression in mixed melting point): Crotonobetaine hydrochloride (1 g.) in benzyl alcohol (4 c.c.) was saturated with dry hydrogen chloride at 0° and the solution kept at room temperature for 16 hours. It was poured into water, and excess of benzyl alcohol was removed and the reineckate prepared as previously (94% yield; m. p. 165—169°) (Found: C, 39·3; H, 5·1; N, 17·5. $C_{18}H_{26}O_2N_7S_4Cr$ requires C, 39·1; H, 4·25; N, 17·7%).

Chloride (X = Cl). A solution of the reineckate in 80% aqueous acetone (30 c.c.) was treated with an aqueous solution of the equivalent amount of silver sulphate. After filtration from silver reineckate, the colourless solution was concentrated to low volume (1/10) under reduced pressure and treated with an aqueous solution of the equivalent amount of barium chloride. After the barium sulphate had settled, the mixture was filtered clear, and the filtrate concentrated under reduced pressure to a syrup which was dried *in vacuo* over phosphoric oxide. The residue was recrystallised from acetone–methanol, yielding the highly hygroscopic cream-coloured *chloride* of low m. p. (45—55°) (Found: Cl, 13·55. $C_{14}H_{20}O_2NCl$ requires Cl, 13·15%).

Iodide (X = I). This *salt*, obtained by treatment of the above chloride in methanol with the equivalent amount of sodium iodide in acetone, had m. p. 149—151° (from methanol) (Found: N, 3·5; I, 35·4. $C_{14}H_{20}O_2NI$ requires N, 3·9; I, 35·2%).

*Trimethyl-(3-carbo-*n*-amyloxyallyl)ammonium Salts* (II; R = *n*-C_5H_{11}).—*Reineckate* [X = $Cr(CNS)_4(NH_3)_2$]. Crude acid chloride of (II; R = H, X = Cl) (0·4 g.) was allowed to react with *n*-amyl alcohol (1·5 c.c.), and the product converted into the *reineckate* following the procedures already described for analogous esters and their salts. This crystallised from acetone–water in pink felted needles, m. p. 157—158° (Found: C, 36·0; H, 5·5; N, 18·9; Cr, 10·7. $C_{16}H_{30}O_2N_7S_4Cr$ requires C, 36·1; H, 5·6; N, 18·4; Cr, 9·8%).

Sulphate (X = $\frac{1}{2}SO_4$). The reineckate (0·35 g.) yielded, by the usual treatment with silver sulphate, the neutral *sulphate* (0·06 g.), m. p. 177° (from methanol) [Found: N, 5·15; SO_4'', 18·8. $(C_{12}H_{24}O_2N)_2SO_4$ requires N, 5·3; SO_4'', 18·3%].

*Trimethyl-(3-carbo-*n*-octyloxyallyl)ammonium Reineckate* [II; R = *n*-C_8H_{17}, X = $Cr(CNS)_4(NH_3)_2$].—Crude acid chloride of (II; R = H, X = Cl) (0·4 g.) was allowed to react with *n*-octyl alcohol (1·5 c.c.) at 80° for 45 minutes. By the appropriate procedure the *reineckate* was obtained and recrystallised from acetone–water, m. p. 156—160° (0·21 g.) (Found: C, 39·7; H, 6·2; N, 17·1; Cr, 9·8. $C_{19}H_{34}O_2N_7S_4Cr$ requires C, 39·8; H, 5·8; N, 17·1; Cr, 9·1%).

When the reineckate was decomposed with silver sulphate solution, the resulting aqueous solution of the sulphate showed the properties of soap solution, and the residue, on evaporation, had the appearance of petroleum jelly.

Trimethyl-(3-carbamylallyl)ammonium Salts (II; NH_2 or OR).—(*a*) Crude acid chloride prepared from crotonobetaine hydrochloride (3 g.) was added in small portions to an excess of aqueous ammonia (*d* 0·880) at 0°. Excess of ammonia was removed by evaporation under reduced pressure at 35° to half volume. Ammonium reineckate was added, precipitating the *reineckate* (5·36 g.), which recrystallised from acetone–water in pink needles, m. p. 174—178° (Found: C, 28·6; H, 5·0. $C_{11}H_{21}ON_8S_4Cr$ requires C, 28·6; H, 4·6%).

(*b*) The methyl ester (II; R = Me, X = Cl) (0·4 g.), prepared by the thionyl chloride route, was dissolved in aqueous ammonia (5 c.c.; *d* 0·880). The solution was freed from ammonia and evaporated in a desiccator. An aqueous solution of the residue yielded the reineckate, m. p. 173—175° (0·6 g.), described in (*a*). This was transformed in the usual way into the *sulphate*, m. p. 203—205° (decomp.). Although analysis of this was not entirely satisfactory [Found: C, 41·9; H, 8·3; N, 13·1 (micro-Dumas), 15·1 (micro-Kjeldahl); SO_4'', 24·2. $(C_7H_{15}ON_2)_2SO_4,H_2O$ requires C, 42·0; H, 8·0; N, 14·0; SO_4'', 24·5%], the material could be reconverted into the reineckate identical with the starting material (Found: C, 28·1; H, 4·7; N, 24·9; Cr, 12·6. Calc. for $C_{11}H_{21}ON_8S_4Cr$: C, 28·6; H, 4·6; N, 24·3; Cr, 11·3%).

The methyl ester (II; R = Me, X = Cl) prepared from crotonobetaine hydrochloride (1 g.) with methanolic hydrogen chloride was treated with excess of concentrated ammonia solution, and the solution evaporated after 1½ hours. The residue was purified from alcohol–ether, yielding the quaternary *chloride* of the amide as a highly deliquescent cream-coloured solid (Found: N, 15·3. $C_7H_{15}ON_2Cl$ requires N, 15·7%). This chloride also yieded the reineckate, m. p. 174—177°, described above.

Trimethyl-[3-(*carbethoxymethylcarbamyl*)*allyl*]*ammonium Salts* (II; $NH{\cdot}CH_2{\cdot}CO_2Et$ for OR)—The crude acid chloride derived from crotonobetaine hydrochloride (1·77 g.) was mixed with finely powdered silica, the granular product thus obtained was added portion-wise during 15 minutes to a stirred solution of glycine ethyl ester (3·9 g.) in dry ether (30 c.c.) at 0°, and stirring was continued at this temperature for half an hour. The solid was filtered off, washed with dry ether, and digested with cold water (100 c.c.). The aqueous extract was filtered clear, made alkaline to litmus with dilute aqueous ammonia, and treated with an aqueous solution of ammonium reineckate. The pink precipitate was collected, washed with water, alcohol, and either, and dried (2·7 g.). Recrystallisation from acetone–water yielded the *reineckate*, m. p. 155—158° (Found: C, 30·7; H, 5·0; N, 20·7; Cr, 10·8. $C_{15}H_{27}O_3N_8S_4Cr$ requires C, 32·9; H, 5·0; N, 20·5; Cr, 9·5%).

An 80% aqueous-acetone solution of this reineckate (2·4 g.) was treated with silver sulphate in the manner already described for conversion into the *sulphate* which was isolated by complete evaporation of the aqueous solution obtained, and reprecipitation of the residue from alcohol by ether. Yield: 0·8 g. of highly deliquescent yellow powder, melting range 90—100° [Found: N, 10·5; SO_4'', 16·0. $(C_{11}H_{21}O_3N_2)_2SO_4$ requires N, 10·1; SO_4'', 17·3%]. It is readily reconverted into the original reineckate in the usual manner, m. p. and mixed m. p. 155—158°.

Trimethyl-(3-*carbethoxy*-2-*ethoxyallyl*)*ammonium Bromide and Reineckate.*—Ethyl γ-bromo-β-ethoxycrotonate (Wohl and Jaschinowski, *loc. cit.*) (2·4 g.) was added to a solution of anhydrous trimethylamine (3·5 g.) in a mixture (24 c.c.) of equal parts of benzene and light petroleum (b. p. 60—80°) in a pressure-bottle and kept at room temperature overnight. The crystalline solid which had separated (2·4 g.) was then recrystallised from acetone–ethyl acetate, giving the desired *bromide*, colourless prisms, m. p. 154—156° (Found: Br, 27·05. $C_{11}H_{22}O_3NBr$ requires Br, 27·0%).

An aqueous solution of this salt deposited the *reineckate* on treatment with ammonium reineckate in the usual way. This formed purple-pink crystals (from acetone–water), m. p. 162—164° (Found: C, 33·0; H, 5·05; N, 17·7. $C_{15}H_{28}O_3N_7S_4Cr$ requires C, 33·7; H, 5·25; N, 18·35%).

RESEARCH DEPARTMENT, ROCHE PRODUCTS LIMITED,
WELWYN GARDEN CITY, HERTS.

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