S 22. *The Preparation of Potential Analgesic Compounds. Part I.*

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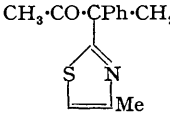
Experiments to obtain compounds of type (IV) (cf. " Amidone," III) or corresponding esters instead of ketones are described. Although (I) was prepared without difficulty, thiazolyl groupings could not be introduced directly into it. On the other hand (VI) and similar compounds were made *via* intermediates such as (V), but then neither ester nor ketone groupings could be introduced on the *tert.*-carbon atom. Approximations to the required objectives were therefore prepared in the form of (IX) and (XII).

In an attempt to extend our knowledge of the interdependence of analgesic response and molecular structure it was desired to prepare ketones typified by (I) (cf. analogous esters, Anker and Cook, *J.*, 1948, 806), and ketones and esters having two strongly basic side chains, typified by compound (II). Secondly, in this connection, the insertion of a thiazole grouping into compounds of type (I) to produce substances comparable with " Amidone " (III), but having one of its phenyl groups replaced by a thiazole ring, was considered. With the spasmolytic and local anæsthetic properties exhibited by basic thiazole derivatives in mind (Chance, Dirnhuber, and Robinson, *Brit. J. Pharmacol. Chemother.*, 1946, **1**, 153), it was possible that these compounds typified by (IV) might be an improvement on " Amidone."

$CH_3 \cdot CO \cdot CHPh \cdot CH_2 \cdot CH_2 \cdot NEt_2$ (I.)

$CH_3 \cdot CO \cdot CPh(CH_2 \cdot CH_2 \cdot NEt_2)_2$ (II.)

$CH_3 \cdot CH_2 \cdot CO \cdot CPh_2 \cdot CH_2 \cdot CHMe \cdot NMe_2$ (III.)



(IV.)

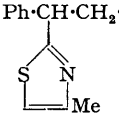
Attempts to prepare the ketones of type (I) were first made by reaction of the appropriate nitriles with Grignard reagents. The basic nitriles, α-diethylaminoethyl- (Eisleb, *Ber.*, 1941, **74**, 1433), α-piperidinoethyl-, and α-morpholinoethyl-benzyl cyanide (Anker and Cook, *loc.*

cit.), were prepared directly from benzyl cyanide and the corresponding 2-chloroethylamine. The conversion into ketones, however, was unsatisfactory, and subsequently direct introduction of the basic side chain into benzyl methyl ketone was performed with the appropriate 2-chloroethylamine and sodamide to give 1-*diethylamino*-3-*phenylpentan*-4-*one* (I), 1-*diethylamino*-3-*phenyl*-2-*methylpentan*-4-*one*, and 1-*morpholino*-3-*phenylpentan*-4-*one*, the last being characterised as its *picrate*.

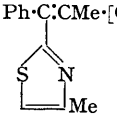
While examining these possibilities, a second basic side chain was introduced into diethylaminoethylbenzyl cyanide by the sodamide–chloroalkylamine method, giving 1 : 5-*bisdiethylamino*-3-*cyano*-3-*phenylpentane*, characterised as its *dipicrate*. The base proved stable to alcoholic sulphuric acid at 150° for 4 hours, so it could not be converted directly into the corresponding ester, and therefore a ketone of type (II) was made otherwise. This was obtained from the sodio-derivative of 1-diethylamino-3-phenylpentan-4-one (I) and *N*-(2-chloroethyl)-diethylamine, which afforded αα-*bis*(*diethylaminoethyl*)*benzyl methyl ketone* (II).

The first approach to the heterocyclic representatives was made by converting diethylaminoethylbenzyl cyanide into γ-diethylamino-α-phenylthiobutyramide (V), characterised as its *hydrochloride*. Attempts to convert this into a thiazole with either chloroacetone or bromoacetal failed. The required thiazole was, however, obtained by condensing phenylthioacetamide, prepared by an improved method from benzyl cyanide, with chloroacetone. 2-*Benzyl*-4-*methylthiazole* (*hydrochloride* and *picrate*) proved to have a sufficiently reactive methylene group to undergo aminoalkylation by reaction of its sodio-derivative with various chloroethyl tertiary amines to give 4-*methyl*-2-(3′-*diethylamino*-1′-*phenylpropyl*)*thiazole* (VI) (and its *dipicrate*), 4-*methyl*-2-(3′-*piperidino*-1′-*phenylpropyl*)*thiazole* (*dipicrate*), 4-*methyl*-2-(3′-*morpholino*-1′-*phenylpropyl*)*thiazole* (*dipicrate*), and 4-*methyl*-2-(3′-*diethylamino*-1′-*phenyl*-2′-*methylpropyl*)*thiazole* (*dipicrate*). It was also found possible to condense the methylene group with 5-diethylaminopentan-4-one in presence of sodium ethoxide to give 4-*methyl*-2-(5′-*diethylamino*-1′-*phenyl*-2′-*methylpent*-1-*enyl*)*thiazole* (VII).

$NEt_2 \cdot CH_2 \cdot CH_2 \cdot CHPh \cdot C(:NH) \cdot SH$ (V.)



(VI.)



(VII.)

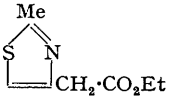
Attempts were then made to introduce a ketone or ester group into 4-methyl-2-(3′-diethylamino-1′-phenylpropyl)thiazole, on the carbon atom carrying the basic side chain, to afford compounds of type (IV). Treatment of the sodium, potassium, or lithium derivatives of the thiazole with ethyl chloroformate, acetyl chloride, ethyl propionate, or ethyl carbonate proved abortive, and even the introduction by these means of a ketonic or ester group into the molecule without a basic side chain (*e.g.*, into 2-benzyl-4-methylthiazole) was unavailing. Preliminary experiments suggested, too, that the latter substance, unlike diphenylmethane, yielded on bromination a mixture of highly brominated with unchanged material, so that the successive introduction of cyano- and ester groups by this means seemed hardly feasible.

Because of the difficulties, an endeavour was made to use simple starting materials already containing an ester or ketone group. The introduction of a diethylaminoethyl group into α-propionylbenzyl cyanide (Bodroux, *Bull. Soc. chim.*, 1910, **7**, 851), however, failed, owing apparently to the almost electrovalent nature of the sodio-derivative of the latter, which made it impossible to attach the required grouping by means of *N*-(2-chloroethyl)diethylamine. To decrease this reactivity it was proposed to convert first the nitrile group into the thioamide and thence into the thiazole, before attempting to put on the basic side chain. α-Propionylbenzyl cyanide was therefore heated with alcoholic sodium hydrogen sulphide. The recovered material, however, proved to be only phenylthioacetamide. Another attempt was made by reaction of the sodio-derivative of benzyl methyl ketone with 2-chlorothiazole (prepared from 2-aminothiazole by the method of McLean and Muir, *J.*, 1942, 384), but here the chlorine atom proved too strongly held to undergo the desired reaction.

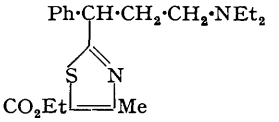
It was thought possible that a substance without the phenyl group might still be an active analgesic agent. *Ethyl* 2-*methylthiazole*-4-*acetate* (VIII) was therefore prepared by condensing thioacetamide with 4-chloroacetoacetic ester (Alexandrow, *Ber.*, 1913, **46**, 1022). The methylene group, however, was here too unreactive to undergo aminoalkylation with *N*-(2-chloroethyl)-diethylamine and sodamide.

Because of all these difficulties, a structural approximation to compounds of type (IV), with a carbethoxy-group attached to the thiazole nucleus instead of to the central carbon

atom, was considered. Condensation of phenylthioacetamide with 2-chloroacetoacetic ester (Dey, *J.*, 1915, **107**, 1646) resulted in 5-*carbethoxy*-2-*benzyl*-4-*methylthiazole* (characterised as its *hydrochloride*). This reacted with chloroethyl *tert.*-amines and sodamide to give, as viscous oils, 5-*carbethoxy*-4-*methyl*-2-(3′-*diethylamino*-1′-*phenylpropyl*)*thiazole* (IX), 5-*carbethoxy*-4-*methyl*-2-(3′-*diethylamino*-1′-*phenyl*-2′-*methylpropyl*)*thiazole*, 5-*carbethoxy*-4-*methyl*-2-(3′-*piperidino*-1′-*phenylpropyl*)*thiazole*, and 5-*carbethoxy*-4-*methyl*-2-(3′-*morpholino*-1′-*phenylpropyl*)*thiazole*.

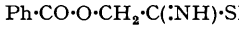


(VIII.)

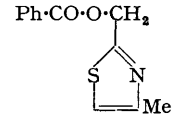


(IX.)

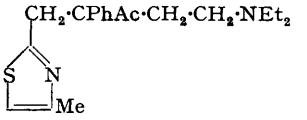
Finally, however, a much nearer approach to compounds of type (IV) was found. Despite the failure to condense 2-chlorothiazole with benzyl methyl ketone mentioned above, it was thought that a chloromethylthiazole might prove more reactive. Starting with the easily accessible benzoyloxythioacetamide (X) (Olin and Johnson, *Rec. Trav. chim.*, 1931, **50**, 72), condensation with chloroacetone gave 4-*methyl*-2-*benzoyloxymethylthiazole* (XI) (*picrate*). The benzoyl group was removed by alkaline hydrolysis and the resulting 4-*methyl*-2-*hydroxymethylthiazole* (*picrate*) converted with thionyl chloride in benzene into 4-*methyl*-2-*chloromethylthiazole* (*hydrochloride* and *picrate*). Reaction with benzyl cyanide in the presence of sodamide gave 4-*methyl*-2-(2′-*cyano*-2′-*phenylethyl*)*thiazole* (*picrate*), though in very small yield. The original thiazole reacted, however, with the sodio-derivative of benzyl methyl ketone to give in good yield 4-*methyl*-2-(2′-*phenylbutan*-3′-*onyl*)*thiazole* (*picrate*), which with *N*-(chloroethyl)diethylamine in the presence of sodamide afforded a good yield of 4-*methyl*-2-(4′-*diethylamino*-2′-*acetyl*-2′-*phenylbutyl*)*thiazole* (XII). Similarly 4-*methyl*-2-(4′-*morpholino*-2′-*acetyl*-2′-*phenylbutyl*)*thiazole* was prepared, though in less satisfactory yield. These last two compounds differ from those of type (IV) only in that the thiazole nucleus is removed from the rest of the molecule by a methylene group.



(X.)



(XI.)



(XII.)

Many of the above compounds were examined for analgesic activity without useful result.

Experimental.

To a stirred solution of benzyl methyl ketone (13·4 g.) and *N*-(2-chloroethyl)diethylamine (13·5 g.) in dry toluene (50 c.c.) was added, during 10 minutes at below 35°, sodamide (3·9 g.). The mixture was gently refluxed for 1½ hours, cooled, and water added. The basic product was isolated by extracting the toluene layer with hydrochloric acid (120 c.c., 2N), basifying with sodium hydroxide, and ether extracting. 1-*Diethylamino*-3-*phenylpentan*-4-*one* was a colourless oil of b. p. 102—105°/0·1 mm., $n_D^{24°}$ 1·4958; yield, 10 g. (Found: C, 77·2; H, 9·85; N, 6·1. $C_{15}H_{23}ON$ requires C, 77·2; H, 9·95; N, 6·0%).

In the same way, from benzyl methyl ketone (13·4 g.) and *N*-(2-chloroethyl)morpholine (15·0 g.), was obtained 1-*morpholino*-3-*phenylpentan*-4-*one*, a colourless oil, b. p. 127—128°/0·01 mm.; 8 g., $n_D^{22°}$ 1·5180 (Found: C, 72·7; H, 8·4; N, 5·45. $C_{15}H_{21}O_2N$ requires C, 72·8; H, 8·6; N, 5·65%). The *picrate* crystallised from ethanol in laths, m. p. 109° (Found: C, 52·7; H, 5·0. $C_{21}H_{24}O_9N_2$ requires C, 52·9; H, 5·1%).

Similarly from benzyl methyl ketone (7·2 g.), *N*-(2-chloropropyl)diethylamine (8 g.), and sodamide (2·1 g.) was obtained 1-*diethylamino*-3-*phenyl*-2-*methylpentan*-4-*one*, b. p. 108°/0·5 mm., $n_D^{23°}$ 1·4953; 3·4 g. (Found: N, 5·4. $C_{16}H_{25}ON$ requires N, 5·65%).

1-Diethylamino-3-phenylpentan-4-one (11 g.), *N*-(2-chloroethyl)diethylamine (7·0 g.), and sodamide (2 g.) were refluxed with stirring in toluene (30 c.c.) for 1½ hours. After cooling, water was added, and the toluene layer fractionated. The highest fraction was αα-*bis*(*diethylaminoethyl*)*benzyl methyl ketone*, b. p. 125°/0·05 mm.; 2 g., $n_D^{22°}$ 1·5010 (Found: C, 75·5; H, 10·9; *M*, by titration with N/20-HCl, 327. $C_{21}H_{36}ON_2$ requires C, 75·8; H, 10·9%; *M*, 332).

2-Diethylaminoethylbenzyl cyanide was prepared according to Eisleb (*loc. cit.*). The *picrate* crystallised from ethanol in flat prisms, m. p. 112° (Found: C, 54·0; H, 5·5. $C_{20}H_{23}O_7N_5$ requires C, 53·9; H, 5·2%).

To a stirred solution of 2-diethylaminoethylbenzyl cyanide (10·8 g.) and *N*-(2-chloroethyl)diethylamine (6·8 g.) in dry benzene (35 c.c.) was added during 10 minutes powdered sodamide (2·0 g.). After 20 minutes below 40°, the suspension was refluxed for one hour. It was cooled, water added, and the benzene layer fractionated. 1 : 5-*Bisdiethylamino*-3-*cyano*-3-*phenylpentane* had b. p. 149—151°/0·1

mm.; 6·5 g. (41%), $n_D^{17°}$ 1·5050 (Found: C, 76·2; H, 10·4; N, 13·4. $C_{20}H_{33}N_3$ requires C, 76·1; H, 10·5; N, 13·3%). The *dipicrate* crystallised from ethanol in deep yellow prisms, m. p. 157° (Found: C, 49·6; H, 5·3. $C_{32}H_{39}O_{14}N_9$ requires C, 49·7; H, 5·1%).

2-Piperidinoethylbenzyl cyanide was prepared directly thus: To benzyl cyanide (15 g.) and *N*-(2-chloroethyl)piperidine (19 g.) in benzene (40 c.c.) was added slowly, with stirring, powdered sodamide (5 g.). The temperature was kept below 35°, but later the mixture was refluxed for 1½ hours, cooled, water added, and the benzene layer fractionated twice. The colourless oil had b. p. 143—146°/0·05 mm.; 15 g. (52%), $n_D^{19°}$ 1·5250. The picrate gave no m. p. depression with that of Anker and Cook (*loc. cit.*); m. p. 160°.

In the same way 2-morpholinoethylbenzyl cyanide was prepared directly: yield 44% of a colourless oil, b. p. 150—154°/0·1 mm., $n_D^{16°}$ 1·5310, $n_D^{23°}$ 1·5280. Identity was established by alcoholysis to ethyl 4-morpholino-2-phenylbutyrate, and the hydrochloride analysed (Found: C, 61·8; H, 7·5. Calc. for $C_{16}H_{24}O_3NCl$: C, 61·3; H, 7·7%).

Diethylaminoethylbenzyl cyanide (5 g.) was sealed with a mixture of saturated alcoholic ammonia (15 c.c.) and alcohol (15 c.c.) which had been saturated at 0° with hydrogen sulphide. After 2 hours' heating at 90°, the alcohol was removed in a vacuum, water added, and the oil extracted with chloroform. The residue on evaporation was triturated with 2N-hydrochloric acid. White *γ-diethylamino-α-phenylthiobutyramide hydrochloride* crystallised from ethanol, m. p. 187°. It gave positive tests for nitrogen, sulphur, and ionic chloride; yield 2·0 g. (Found: S, 11·7. $C_{14}H_{23}N_2ClS$ requires S, 11·2%).

To benzyl cyanide (36 g.) in alcohol (280 c.c.) was added sodium hydroxide (28 g.) in water (55 c.c.), and the mixture saturated with hydrogen sulphide at 0°. After standing at room temperature for 3 days, the solution was refluxed while a swift stream of hydrogen sulphide was passed through it for 3 hours. It was cooled, and poured into ice and water (1·5 l.). The oil solidified, and was filtered off and treated on a porous tile when necessary; yield of phenylthioacetamide, dried over sulphuric acid, 26 g. (58%). It was purified by dissolving in boiling benzene (160 c.c.), filtering, and adding petroleum (b. p. 100—120°, 190 c.c.). The precipitated material was redissolved by heating and deposited in long needles, m. p. 97—98° (lit., m. p. 97·5°).

Phenylthioacetamide (22·5 g.) and chloroacetone (11·3 c.c.) in dry alcohol (100 c.c.) were refluxed for ½ hour after the initial vigorous reaction. The condenser was removed, and the bath temperature raised to 115—120° for 2 hours. The residue solidified on scratching and cooling. Recrystallisation from dioxan (80 c.c.) gave white, slightly hygroscopic, plates of 2-*benzyl*-4-*methylthiazole hydrochloride*, m. p. 122—123°; 21 g., 62% (Found: C, 57·5; H, 5·4. $C_{11}H_{12}NClS$ requires C, 57·5; H, 5·4%). This hydrochloride (19 g.), treated in aqueous solution with sodium hydroxide, gave 13·7 g. of 2-*benzyl*-4-*methylthiazole*, b. p. 94—96°/0·1 mm., $n_D^{18°}$ 1·5812 (Found: C, 70·2; H, 5·9. $C_{11}H_{11}NS$ requires C, 69·9; H, 5·9%). The *picrate* crystallised from ethanol in plates, m. p. 121° (Found: C, 48·9; H, 3·5. $C_{17}H_{14}O_7N_4S$ requires C, 48·8; H, 3·4%).

2-Benzyl-4-methylthiazole (7·4 g.) and *N*-(2-chloroethyl)diethylamine (5·7 g.) were mixed in dry toluene (40 c.c.), and powdered sodamide (1·6 g.) added with mechanical stirring. The temperature was slowly raised to boiling and kept there for 1½ hours. On cooling, water (30 c.c.) was added to dissolve salts, and the toluene layer separated and dried. The second fraction on distillation was 4-*methyl*-2-(3′-*diethylamino*-1′-*phenylpropyl*)*thiazole*, a colourless oil, b. p. 125°/0·1 mm.; 3·1 g., $n_D^{18°}$ 1·5425 (Found: C, 71·0; H, 8·5. $C_{17}H_{24}N_2S$ requires C, 70·8; H, 8·4%). The *dipicrate* crystallised from ethanol in stout needles, m. p. 142° (Found: C, 46·8; H, 4·0. $C_{29}H_{30}O_{14}N_8S$ requires C, 46·7; H, 4·0%).

In the same way from 2-benzyl-4-methylthiazole (7·4 g.) and *N*-(2-chloroethyl)piperidine (5·9 g.) were obtained 2·3 g. of 4-*methyl*-2-(2′-*piperidino*-1′-*phenylpropyl*)*thiazole*, b. p. 140—143°/0·1 mm., $n_D^{18°}$ 1·5614 (Found: C, 71·5; H, 7·7; N, 9·1. $C_{18}H_{24}N_2S$ requires C, 71·9; H, 8·0; N, 9·3%). The *dipicrate*, from ethanol, had m. p. 180° (Found: C, 47·5; H, 4·1. $C_{30}H_{30}O_{14}N_8S$ requires C, 47·5; H, 4·0%).

Similarly, from 2-benzyl-4-methylthiazole (7·6 g.) and *N*-(2-chloroethyl)morpholine (6·2 g.) with sodamide (1·7 g.) were obtained 2·2 g. of 4-*methyl*-2-(3′-*morpholino*-1′-*phenylpropyl*)*thiazole*, b. p. 145—148°/0·05 mm., $n_D^{19°}$ 1·5640 (Found: C, 67·3; H, 7·5; N, 9·3. $C_{17}H_{22}ON_2S$ requires C, 67·5; H, 7·3; N, 9·3%). The *dipicrate* from ethanol formed deep yellow, stout crystals, m. p. 170° (Found: C, 45·8; H, 3·8. $C_{29}H_{28}O_{15}N_8S$ requires C, 45·8; H, 3·7%).

By the same method from 2-benzyl-4-methylthiazole (7·3 g.) and *N*-(2-chloropropyl)diethylamine (5·8 g.) was isolated 4-*methyl*-2-(3′-*diethylamino*-1′-*phenyl*-2′-*methylpropyl*)*thiazole*; 3·1 g., b. p. 128—130°/0·1 mm., $n_D^{23°}$ 1·5380 (Found: C, 71·5; H, 8·6; N, 9·2. $C_{18}H_{26}N_2S$ requires C, 71·5; H, 8·7; N, 9·3%). The *dipicrate*, crystallised from ethanol, had m. p. 139—140° (Found: C, 47·6; H, 4·4. $C_{30}H_{32}O_{14}N_8S$ requires C, 47·4; H, 4·2%).

2-Benzyl-4-methylthiazole (5·7 g.) and 5-diethylaminopentan-2-one (4·7 g.) were refluxed in dry alcohol (20 c.c.) in which sodium (0·6 g.) had been dissolved, for 2 hours. On cooling, the solution was poured into ice-water (80 c.c.), and the oil removed in ether. The yellow oily 4-*methyl*-2-(5′-*diethylamino*-1′-*phenyl*-2′-*methylpent*-1′-*enyl*)*thiazole* (0·9 g.) had b. p. 145°/0·1 mm., $n_D^{18°}$ 1·4920 (Found: N, 8·3. $C_{20}H_{28}N_2S$ requires N, 8·5%).

Action of Sodium Hydrogen Sulphide on α-Propionylbenzyl Cyanide.—α-Propionylbenzyl cyanide (4 g.), prepared according to Bodroux (*loc. cit.*), was added to a solution of sodium hydrogen sulphide (from sodium hydroxide 3 g., in water 6 c.c., and alcohol 30 c.c.). The solution was again saturated with hydrogen sulphide at 0° (pH 6—7). It was sealed and heated to 100° for 2 hours. The pH on opening was *ca.* 8. After addition of water, the oil was extracted with chloroform, dried, and evaporated; a solid remained, and treatment on a porous tile gave 1·1 g. of a white solid, m. p. 95°. Recrystallisation from benzene–petroleum gave needles, m. p. 98—99° (Found: C, 63·3; H, 6·0; S, 21·4. Calc. for C_8H_9NS: C, 63·5; H, 6·0; S, 21·2%), which gave no depression with authentic phenylthioacetamide prepared from benzyl cyanide in the same way.

Thioacetamide (51 g.), 4-chloroacetoacetic ester (110 g.; Alexandrow, *loc. cit.*), pyridine (65 c.c.), and dry alcohol (120 c.c.) with a little sodium iodide were heated gradually to about 100° under reflux; a vigorous reaction took place, requiring immediate cooling in ice–water. After ½ hour's refluxing, the

condenser was removed, and the flask heated in an oil-bath at 115° for 1 hour to remove some of the alcohol. The residue was cooled, poured into ice-water (250 c.c.), and the oil extracted with ether. Two distillations gave *ethyl 2-methylthiazole-4-acetate* as a clear, slightly yellow oil (65 g.), b. p. 82—83°/0·1 mm., $n_D^{19°}$ 1·5110 (Found: C, 51·4; H, 6·1; N, 7·8. $C_8H_{11}O_2NS$ requires C, 51·9; H, 6·0; N, 7·6%). The substance was very weakly basic but gave a hygroscopic hydrochloride from ether.

Phenylthioacetamide (43 g.), 2-chloroacetoacetic ester (50 g.; Dey, *loc. cit.*), and dry alcohol (90 c.c.) containing a little sodium iodide were heated under reflux at 100°, until the first vigour of reaction subsided. The condenser was removed, and the bath raised to 110—115° for 1½ hours. The hydrochloride solidified on cooling and scratching. It was broken up in a mixture of sodium carbonate solution (15 g./200 c.c.) and ether (150 c.c.). Two clean layers gradually formed. After a second extraction, the ethereal solution was well dried (Na_2SO_4), and the hydrochloride reprecipitated with hydrogen chloride to remove non-basic material. It was filtered off, washed with dry ether, and converted into the base again as above. *5-Carbethoxy-2-benzyl-4-methylthiazole* distilled as a yellow oil (27 g.), b.p. 141—144°/0·02 mm., $n_D^{20°}$ 1·5650 (Found: C, 64·4; H, 5·5; N, 5·45. $C_{14}H_{15}O_2NS$ requires C, 64·3; H, 5·8; N, 5·35%). The *hydrochloride*, from the distilled base, crystallised from dioxan in a felt-like mass of needles, m. p. 145°, soluble only in concentrated hydrochloric acid (Found: N, 4·9. $C_{14}H_{16}O_2NClS$ requires N, 4·7%).

5-Carbethoxy-2-benzyl-4-methylthiazole (7·8 g.) and *N*-(2-chloroethyl)diethylamine (4·4 g.) were mixed with toluene (30 c.c.) and powdered sodamide (1·2 g.), and gently refluxed for 3 hours. The mixture was cooled, and water (30 c.c.) added to dissolve salt. The toluene layer was extracted with acetic acid (7%, 4 × 50 c.c.) to separate weakly basic unchanged thiazole from the strongly basic product. The extract was made well alkaline with sodium hydroxide solution (ice added), and the oil extracted with ether. *5-Carbethoxy-4-methyl-2-(3′-diethylamino-1′-phenylpropyl)thiazole* was a yellow oil, b. p. 155—158°/0·1 mm., $n_D^{22°}$ 1·5390; 2·1 g. (Found: C, 66·2; H, 7·7; N, 7·9. $C_{20}H_{28}O_2N_2S$ requires C, 66·6; H, 7·8; N, 7·8%).

In a similar way from 5-carbethoxy-2-benzyl-4-methylthiazole (7·8 g.) and *N*-(2-chloropropyl)-diethylamine (4·7 g.) was obtained *5-carbethoxy-4-methyl-2-(3′-diethylamino-1′-phenyl-2′-methylpropyl)-thiazole*; 2·7 g., b. p. 175—177°/0·05 mm., $n_D^{18°}$ 1·5338 (Found: C, 67·2; H, 8·1; N, 7·5. $C_{21}H_{30}O_3N_2S$ requires C, 67·3; H, 8·1; N, 7·5%).

Likewise, from 5-carbethoxy-2-benzyl-4-methylthiazole (15·6 g.), *N*-(2-chloroethyl)piperidine (9·7 g.), and sodamide (2·5 g.) in toluene (60 c.c.), was obtained *5-carbethoxy-4-methyl-2-(3′-piperidino-1′-phenylpropyl)thiazole*, b. p. 173—175°/10^{-3} mm.; 4 g., $n_D^{16°}$ 1·5545 (Found: N, 7·5. $C_{21}H_{28}O_2N_2S$ requires N, 7·5%).

Similarly, from 5-carbethoxy-2-benzyl-4-methylthiazole (11·9 g.), *N*-(2-chloroethyl)morpholine (8·1 g.), and sodamide (1·8 g.) were obtained 2·0 g. of *5-carbethoxy-4-methyl-2-(3′-morpholino-1′-phenylpropyl)thiazole*, b. p. 178—182°/0·05 mm., $n_D^{18°}$ 1·5586 (Found: C, 63·5; H, 7·0; N, 7·5. $C_{20}H_{26}O_3N_2S$ requires C, 64·1; H, 7·0; N, 7·5%).

Benzoyloxythioacetamide (125 g.; Olin and Johnson, *loc. cit.*), chloroacetone (55 c.c.), pyridine (50 c.c.), dry alcohol (250 c.c.), and a little sodium iodide were refluxed on a steam-bath for 1½ hours, then cooled, poured into ice-water, and the oil removed with ether. Distillation gave 90 g. of a red oil containing some solid material; boiling range, 130—160°/0·1 mm. This material is best used directly for conversion into 4-methyl-2-hydroxymethylthiazole. A sample was purified by precipitating the hydrochloride from dry ether and regenerating the base. Pure *4-methyl-2-benzoyloxymethylthiazole* had b. p. 125—127°/0·1 mm., and distilled as a clear yellow oil, $n_D^{20°}$ 1·5702 (Found: N, 6·0. $C_{12}H_{11}O_2NS$ requires N, 6·0%). The *picrate* crystallised in long needles from ethanol, m. p. 145° (Found: C, 47·0; H, 2·95. $C_{18}H_{14}O_9N_4S$ requires C, 46·8; H, 3·05%).

The crude 4-methyl-2-benzoyloxymethylthiazole (64 g.) was hydrolysed with sodium hydroxide (14 g.) and water (75 c.c.) by refluxing vigorously over a gauze for 1 hour, the layers then having disappeared. The foul-smelling solution was extracted 6 times with ether (150 c.c. each). *4-Methyl-2-hydroxymethylthiazole* had b. p. 86°/0·1 mm.; 22 g., $n_D^{22°}$ 1·5495 (Found: C, 46·9; H, 5·8; N, 10·8. C_5H_7ONS requires C, 46·5; H, 5·5; N, 10·8%). The *picrate* formed stout prisms from ethanol, m. p. 132° (Found: C, 37·3; H, 2·9. $C_{11}H_{10}O_8N_4S$ requires C, 36·9; H, 2·8%).

To 4-methyl-2-hydroxymethylthiazole (60 g.) in dry benzene (120 c.c.), stirred and maintained below room temperature, was added thionyl chloride (45 c.c.) in benzene (100 c.c.). After 50 mins.' heating on the water-bath, all volatile matter was removed at the water pump while still warming. The solid was dissolved in water, neutralised with sodium hydrogen carbonate, and the base extracted with ether. *4-Methyl-2-chloromethylthiazole* distilled as a colourless liquid (56 g.), darkening in a few days; b. p. 92°/20 mm., $n_D^{21°}$ 1·5442 (Found: N, 9·6. C_5H_6NClS requires N, 9·5%). The liquid is a powerful skin irritant, but is not lachrymatory. The *hydrochloride*, from dry ether, crystallised in clusters of stout needles from dioxan; m. p. 152° (Found: N, 7·6. $C_5H_7NCl_2S$ requires N, 7·6%). The *picrate* formed large crystals from ethanol; m. p. 120° (Found: N, 14·9. $C_{11}H_9O_7N_4ClS$ requires N, 14·9%).

Powdered sodamide (3·9 g.) was added slowly with stirring to a mixture of benzyl methyl ketone (13·4 g.) and 4-methyl-2-chloromethylthiazole (14·8 g.) in toluene (50 c.c.). The temperature was kept below 40° for 30 minutes and then gradually raised. After 2 hours' gentle refluxing, the mixture was cooled, water added, and the toluene layer dried and distilled. The fraction, b. p. 130—145°/0·2 mm., was redistilled. Pure *4-methyl-2-(2′-phenylbutan-3′-onyl)thiazole* had b. p. 127°/0·05 mm., $n_D^{26°}$ 1·5610 (Found: C, 69·1; H, 6·3; N, 5·8. $C_{14}H_{15}ONS$ requires C, 68·6; H, 6·2; N, 5·7%). The *picrate* crystallised as plates from ethanol, m. p. 117° (Found: N, 11·7. $C_{20}H_{18}O_8N_4S$ requires N, 11·8%).

4-Methyl-2-(2′-phenylbutan-3′-onyl)thiazole (12·8 g.) and *N*-(2-chloroethyl)diethylamine (7·4 g.), dissolved in toluene (40 c.c.), were treated while being stirred with powdered sodamide (2·2 g.). After 30 minutes below 35°, the temperature was raised until the toluene gently refluxed and was kept there for 2½ hours. The mixture was cooled, water added, and the strongly basic product extracted from the toluene with acetic acid (2N, 50 c.c.). The base was liberated with sodium hydroxide, extracted with ether, and distilled. *4-Methyl-2-(4′-diethylamino-2′-acetyl-2′-phenylbutyl)thiazole* was a yellow oil (8 g.), b. p. 152—155°/0·01 mm., $n_D^{22°}$ 1·5478 (Found: N, 8·1. $C_{20}H_{28}ON_2S$ requires N, 8·1%).

In the same way from 4-methyl-2-(2′-phenylbutan-3′-onyl)thiazole (12·2 g.), *N*-(2-chloroethyl)-morpholine (7·5 g.), and sodamide (2·0 g.) was prepared 4-*methyl*-2-(4′-*morpholino*-2′-*acetyl*-2′-*phenylbutyl*)*thiazole* (1·8 g.); b. p. 180°/0·1 mm., $n_D^{21°}$ 1·5648 (Found : C, 66·8; H, 7·1; N, 8·1. $C_{20}H_{26}O_2N_2S$ requires C, 67·0; H, 7·3; N, 7·8%).

To benzyl cyanide (13·5 g.) and 4-methyl-2-chloromethylthiazole (17 g.) in toluene (50 c.c.) was added with stirring, powdered sodamide (4·7 g.), and the temperature was raised after 20 minutes to boiling for 2½ hours. After cooling, water was added and the toluene layer fractionated. The crude distillate boiling *ca.* 150°/0·5 mm. amounted to 4 g. and contained a little solid. It was purified through the hydrochloride from dry ether, and 4-*methyl*-2-(2′-*cyano*-2′-*phenylethyl*)*thiazole* had b. p. 133°/0·1 mm., $n_D^{21°}$ 1·5717 (Found : C, 68·2; H, 5·3; N, 12·0. $C_{13}H_{12}N_2S$ requires C, 68·4; H, 5·3; N, 12·3%). The *picrate* crystallised from ethanol in small prisms, m. p. 137—138° (Found : C, 50·2; H, 3·3. $C_{19}H_{15}O_7N_5S$ requires C, 49·9; H, 3·3%).

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