S 23. *The Preparation of Potential Analgesic Compounds. Part II.*

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Compounds of potential analgesic properties were obtained from ethyl α-cyanophenylacetate by converting it into the corresponding thio-amide and thence into 4-*phenyl*- and 4-*methyl*-2-α-*carbethoxybenzylthiazole* (*e.g.*, V). Introduction of basic groups into the latter compounds gave bases typified by (VI) and comparable with " Amidone " (II).

The preceding communication dealt in part with attempts to introduce a thiazole grouping into ketones of the type of (I) in order to obtain substances comparable with " Amidone " (II), but with one phenyl group replaced by a thiazole ring. Of the several methods which were investigated, that by way of (III) from propionylbenzyl cyanide failed because of the loss of the propionyl group during thio-amide formation. It was considered that this difficulty might not arise if the propionyl were replaced by the carbethoxy-group as in (IV). This proved to be correct, and thus the way was opened to compounds typified by (VI).

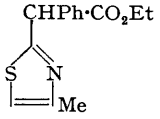
$NEt_2 \cdot CH_2 \cdot CH_2 \cdot CHPh \cdot COMe$ (I.)

$NMe_2 \cdot CHMe \cdot CH_2 \cdot CPh_2 \cdot COEt$ (II.)

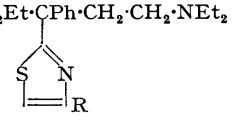
$Et \cdot CO \cdot CHPh \cdot C(:NH) \cdot SH$ (III.)

$CO_2Et \cdot CHPh \cdot CH(:NH) \cdot SH$ (IV.)

Ethyl α-cyanophenylacetate was prepared by the direct carbethoxylation of benzyl cyanide (Nelson, *J. Amer. Chem. Soc.*, 1928, **50**, 2758). It was converted in good yield by the action of hydrogen sulphide in the presence of triethanolamine into α-*carbethoxyphenylthioacetamide*, which reacted with chloroacetone to form the solid 2-α-*carbethoxybenzyl*-4-*methylthiazole* (V) in 33% yield. Similarly with chloroacetophenone, liquid 4-*phenyl*-2-α-*carbethoxybenzylthiazole* (characterised as *hydrochloride*) was produced. In an endeavour to increase the yield with chloroacetone the reactants were heated finally at 110°. The carbethoxyl group, however, was lost thereby, and the main product was 2-benzyl-4-methylthiazole. 2-α-Carbethoxybenzyl-4-methylthiazole condensed with *N*-(2-chloroethyl)diethylamine in the presence of sodamide to give 2-(3′-*diethylamino*-1′-*carbethoxy*-1′-*phenylpropyl*)-4-*methylthiazole* (VI; R = Me), characterised as its *dipicrate*; and similarly, by using the appropriate chloroalkylamine, were obtained 2-(3′-*diethylamino*-1′-*carbethoxy*-1′-*phenyl*-2′-*methylpropyl*)-, 2-(3′-*morpholino*-1′-*carbethoxy*-1′-*phenylpropyl*)- (characterised as its *oxalate*), and, in less satisfactory yield, 2-(3′-*morpholino*-1′-*carbethoxy*-1′-*phenyl*-2′-*methylpropyl*)-4-*methylthiazole*. The N-(2-*chloropropyl*)-*morpholine*, characterised as its *picrate*, required for the preparation of the last compound, was formed by the action of thionyl chloride on 1-*morpholinopropan*-2-*ol* (*hydrochloride*), itself made from morpholine and propylene oxide. By similar condensations, 4-phenyl-2-α-carbethoxybenzylthiazole afforded 4-*phenyl*-2-(3′-*diethylamino*-1′-*carbethoxy*-1′-*phenyl*-2′-*methylpropyl*)-*thiazole*, and 4-*phenyl*-2-(3′-*diethylamino*-1′-*carbethoxy*-1′-*phenylpropyl*)*thiazole* (VI; R = Ph).



(V.)



(VI.)

Most of these compounds containing ester, phenyl, thiazole, and a second basic grouping were tested for analgesic action but with negative result.

Experimental.

Triethanolamine (7·0 c.c.) in ethanol (140 c.c.) was saturated with hydrogen sulphide. Ethyl α-cyanophenylacetate (120 g.) was added, and hydrogen sulphide passed in at 45° for 10 hrs. The mixture was cooled and seeded. The crystalline precipitate was collected, and most of the ethanol removed from the filtrate on the steam-bath in a vacuum. Fresh ethanol (30 c.c.) was added, hydrogen sulphide passed in again, and a second crop, and ultimately a third, was obtained. The total yield after crystallisation from benzene was 65 g. (45%). *α-Carbethoxyphenylthioacetamide* formed small needles, m. p. 121° (Found : C, 58·7; H, 5·8; N, 6·15. $C_{11}H_{13}O_2NS$ requires C, 59·1; H, 5·9; N, 6·25%).

Chloroacetone (5·5 c.c.), α-carbethoxyphenylthioacetamide (15 g.), dry pyridine (6·5 c.c.), and a little sodium iodide were dissolved in ethanol (30 c.c.) on the steam-bath. The mixture was refluxed for 2 hrs., cooled, poured into water, and the oil taken up in ether. A small amount of unchanged thio-amide sometimes separated and was filtered off. The fraction, b. p. 135—140°/0·2 mm., solidified and was recrystallised from light petroleum, forming colourless needles. *2-α-Carbethoxybenzyl-4-methylthiazole* (yield 5·8 g.) had m. p. 67—68° (Found : C, 64·25; H, 5·8; N, 5·3. $C_{14}H_{15}O_2NS$ requires C, 64·35; H, 5·8; N, 5·4%).

N-(2-Chloroethyl)diethylamine (3·8 g.), 2-carbethoxybenzyl-4-methylthiazole (6·7 g.), and powdered sodamide (1·1 g.) were stirred in dry toluene (30 c.c.). After 20 minutes at 35—40°, the mixture was refluxed with stirring for 2 hrs. On cooling, water was added, and the toluene layer extracted with 5% acetic acid (2 × 40 c.c.). The base was liberated with aqueous sodium hydroxide, extracted with ether, and distilled. *2-(3′-Diethylamino-1′-carbethoxy-1′-phenylpropyl)-4-methylthiazole* (3·6 g.) was a yellow oil, b. p. 160—163°/0·1 mm., $n_D^{20°}$ 1·5374 (Found : C, 67·0; H, 7·85; N, 8·0. $C_{20}H_{28}O_2N_2S$ requires C, 66·6; H, 7·85; N, 7·8%). The *dipicrate* formed small laths, m. p. 122°, from ethanol (Found : C, 47·1; H, 4·4. $C_{32}H_{34}O_{16}N_8S$ requires C, 46·9; H, 4·2%).

In a similar way, from *N*-(2-chloropropyl)diethylamine (3·3 g.), 2-α-carbethoxybenzyl-4-methylthiazole (5·2 g.), and sodamide (0·9 g.) was obtained *2-(3′-diethylamino-1′-carbethoxy-1′-phenyl-2′-methylpropyl)-4-methylthiazole* as a yellow oil, b. p. 165°/0·2 mm., $n_D^{17°}$ 1·5388 (Found : C, 67·5; H, 8·15; N, 7·4. $C_{21}H_{30}O_2N_2S$ requires C, 67·3; H, 8·05; N, 7·5%).

Likewise, *N*-(2-chloroethyl)morpholine (6·4 g.), 2-α-carbethoxybenzyl-4-methylthiazole (10·0 g.), and sodamide (1·7 g.) in toluene (70 c.c.) afforded *2-(3′-morpholino-1′-carbethoxy-1′-phenylpropyl)-4-methylthiazole* (1·4 g.), b. p. 181—183°/0·05 mm., as a very viscous yellow oil, $n_D^{21°}$ 1·5570 (Found : C, 64·1; H, 7·3; N, 7·7. $C_{20}H_{26}O_3N_2S$ requires C, 64·1; H, 7·0; N, 7·5%). The *oxalate* was precipitated from ethereal oxalic acid and recrystallised from dioxan, forming micro-needles, m. p. 165° (Found : N, 5·85. $C_{22}H_{28}O_7N_2S$ requires N, 6·0%).

Propylene oxide (58 g.) was mixed under reflux with morpholine (86 g.) and methanol (20 c.c.). After 20 mins. the mixture was gently boiling and when it began to cool, in about 3 hrs., it was refluxed for a further hour on the steam-bath. *1-Morpholinopropan-2-ol* (120 g., 83%) had b. p. 97—98°/13 mm. $n_D^{24°}$ 1·4621 (Found : N, 9·6. $C_7H_{15}O_2N$ requires N, 9·65%). The *hydrochloride*, precipitated from dry ether and recrystallised from dioxan, formed colourless, rectangular, very hygroscopic crystals, m. p. 125—126° (Found : N, 7·7. $C_7H_{16}O_2NCl$ requires N, 7·7%).

1-Morpholinopropan-2-ol (36 g.) was dissolved in dry benzene (150 c.c.) and, with stirring at 5°, thionyl chloride (30 c.c.) in benzene (120 c.c.) was added dropwise. The mixture was refluxed for 1 hour on the steam-bath with stirring and then evaporated to dryness in a vacuum on the steam-bath. The solid was dissolved in water (100 c.c.), filtered from a little tar, the solution basified with sodium hydroxide, and the product removed in ether. *N-(2-Chloropropyl)morpholine* distilled as a faintly yellow liquid (30 g., 74%), b. p. 88—89°/15 mm., $n_D^{22°}$ 1·4681 (Found : N, 8·55. $C_7H_{14}ONCl$ requires N, 8·55%). The *picrate*, from ethanol, formed large stout needles, m. p. 114—115° (Found : N, 14·0. $C_{13}H_{17}O_8N_4Cl$ requires N, 14·3%).

N-(2-Chloropropyl)morpholine (7·0 g.), 2-α-carbethoxybenzyl-4-methylthiazole (10 g.), and sodamide (1·7 g.) were brought into reaction as described above for the corresponding diethylamino-compound. *2-(3′-Morpholino-1′-carbethoxy-1′-phenyl-2′-methylpropyl)-4-methylthiazole* was a thick yellow oil (yield, 0·6 g.), b. p. 187—190°/0·1 mm., $n_D^{21°}$ 1·5528 (Found : C, 64·4; H, 7·15; N, 7·35. $C_{21}H_{28}O_3N_2S$ requires C, 64·9; H, 7·25; N, 7·2%).

A mixture of α-carbethoxyphenylthioacetamide (9·0 g.), chloroacetophenone (6·2 g.), dry pyridine (4 c.c.), ethanol (20 c.c.), and a little iodide as catalyst was heated on the steam-bath under reflux for 1 hr. The cooled liquid was poured into water (50 c.c.), and the oil removed in ether. Distillation gave *4-phenyl-2-α-carbethoxybenzylthiazole* (4·7 g.) as a viscous liquid, b. p. 166—168°/0·05 mm., $n_D^{16°}$ 1·6171 (Found : N, 4·3. $C_{19}H_{17}O_2NS$ requires N, 4·3%). The *hydrochloride*, from dry ether, crystallised from dioxan in small, hygroscopic prisms, m. p. 111° (Found : N, 4·1. $C_{19}H_{18}O_2NSCl$ requires N, 3·9%).

To *N*-(2-chloroethyl)diethylamine (3·0 g.) and 4-phenyl-2-α-carbethoxybenzylthiazole (6·5 g.) in dry toluene (30 c.c.) was added powdered sodamide (0·9 g.), and the suspension boiled with stirring for 2 hrs. On cooling, water (40 c.c.) was added, and the strongly basic product removed from the toluene layer with 5% acetic acid (100 c.c.). The base, liberated again with ice-cold aqueous sodium hydroxide, was extracted with ether and distilled. *4-Phenyl-2-(3′-diethylamino-1′-carbethoxy-1′-phenylpropyl)thiazole* was a clear oil (1·6 g.), b. p. 197—200°/0·05 mm., $n_D^{19°}$ (Found : C, 71·2; H, 7·2; N, 6·85. $C_{25}H_{30}O_2N_2S$ requires C, 71·1; H, 7·2; N, 6·65%).

In the same way, from *N*-(2-chloropropyl)diethylamine (3·4 g.), 4-phenyl-2-α-carbethoxybenzylthiazole (6·7 g.), and sodamide (1·0 g.), was produced 0·6 g. of the clear yellow oil, *4-phenyl-2-(3′-diethylamino-1′-carbethoxy-1′-phenyl-2′-methylpropyl)thiazole*, $n_D^{19°}$ 1·5785 (Found : N, 6·2. $C_{26}H_{32}O_2N_2S$ requires N, 6·4%).

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