arated by filtration and purified by recrystallization from 2-propanol to give 0.65 g. of colorless prisms.

3,5-Dimethylpyrazole-1-acetamide. C.—To 4.3 g. (0.11 mole) of sodamide was added a solution of 9.6 g. (0.1 mole) of 3,5-dimethylpyrazole in 100 ml. of dry benzene. The reaction mixture was heated under reflux for 30 min. To the mixture was then added 9.4 g. (0.1 mole) of chloracetamide and refluxing was continued for 1 hr. The mixture was allowed to cool to room temperature and was filtered. The solid was slurried with hot chloroform, filtered, and the filtrate evaporated to dryness. The residue was recrystallized from ethanol.

β-(3,5-Dimethylpyrazole-1)propiophenone.—A mixture of 17.7 g. (0.1 mole) of β-dimethylaminopropiophenone and 9.67 g. of 3,5-dimethylpyrazole was heated on a steam bath for 3 hr. The mixture, which partially solidified upon cooling, was triturated with a small amount of petroleum ether. The solid was removed by filtration and recrystallized from petroleum ether (Skellysolve B).

3,5-Diethylpyrazole-1-carboxamide.—To a solution of 11.2 g. (0.1 mole) of semicarbazide hydrochloride in 30 ml. of water was added a solution of 12.8 g. (0.1 mole) of 3,5-heptanedione in 10 ml. of ethanol over a period of 10 min. Stirring was continued for 4 hr., the solid removed by filtration, and purified by recrystallization.

N-Butyl-3,5-dimethylpyrazole-1-carboxamide.—A mixture of 9.6 g. (0.1 mole) of 3,5-dimethylpyrazole and 19.8 g. (0.2 mole) of *n*-butyl isocyanate was heated on the steam bath for 1 hr. To the reaction mixture was then added 25 ml. of ether and the ethereal solution washed with 25 ml. of 5% sodium carbonate solution and then with 25 ml. of water. Removal of the ether gave a colorless oil which solidified upon standing.

3,5-Dimethylpyrazole-1-carboxylic Acid Hydrazide.—To a solution of 9.0 g. (0.1 mole) of carbohydrazide in 35 ml. of water at 15° was added a solution of 10.0 g. (0.1 mole) of 2,4-pentanedione in 5 ml. of ethanol and the mixture stirred at 10–15° for 30 min. The mixture was extracted 3 times with 10-ml. portions of ether. The aqueous layer on standing overnight precipitated a colorless solid. This was removed by filtration, washed with cold water and ether, and purified by recrystallization from ether.

***p*-(3,5-Dimethylpyrazole-1)benzoic Acid.**—A mixture of 9.55 g. (0.096 mole) of 2,4-pentanedione, 14.55 g. (0.096 mole) of *p*-hydrazinobenzoic acid, 7.84 g. (0.096 mole) of anhydrous sodium acetate, 10 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. The mixture was cooled in an ice bath and neutralized with concentrated hydrochloric acid. The solid was filtered, washed with water, and recrystallized from ethyl acetate.

***p*-(3,5-Dimethylpyrazole-1)benzamide. D.**—A stirred mixture of 4.0 g. (0.0185 mole) of *p*-(3,5-dimethylpyrazolyl-1)benzoic acid, 3.3 g. (0.028 mole) of thionyl chloride and 100 ml. of dry benzene was heated under reflux for 1.25 hr. The hot mixture was filtered and the solid washed with ether. The filtrate and ether were concentrated *in vacuo* on a steam bath. Two 50-ml. portions of benzene were added and then were removed *in vacuo* on a steam bath. To the crude acid chloride was added 6 ml. of concentrated ammonium hydroxide and the mixture stirred for 1 hr. The mixture was diluted with water and filtered. The cake was washed with water and purified by recrystallization.

1-(*p*-Sulfamylphenyl)-3,5-dimethylpyrazole.—A stirred mixture of 19.88 g. (0.106 mole) of *p*-sulfamylphenyl hydrazine,[5] 8.70 g. (0.106 mole) of 2,4-pentanedione, 60 ml. of ethanol, and 25 ml. of water was heated under reflux for 1 hr. The mixture was then neutralized by the addition of 8.7 ml. of concentrated hydrochloric acid, the solid removed by filtration, and washed with ethanol.

***p*-(3,5-Dimethyl-1-pyrazolyl)benzenesulfonylurea.**—A mixture of 4.0 g. (0.016 mole) of 1-(*p*-sulfamylphenyl)-3,5-dimethylpyrazole, 1.3 g. (0.016 mole) of potassium cyanate, 20 ml. of ethanol, and 5 ml. of water was heated under reflux for 7 hr. The unchanged starting material (0.68 g.) was removed by filtration and the filtrate concentrated to dryness. The residue was diluted with 15 ml. of water and acidified with acetic acid. The resulting solid was collected by filtration and purified by recrystallization.

1-(*p*-Chlorobenzoyl)-3,5-dimethylpyrazole.—To a slurry of 9.6 g. (0.1 mole) of 3,5-dimethylpyrazole in 100 ml. of anhydrous ether at 10–15° was added dropwise with stirring 8.7 g. (0.05 mole) of *p*-chlorobenzoylchloride. The mixture was stirred at room temperature for 1 hr. and then filtered. The filtrate was washed with water, dried, concentrated, and the residue distilled under vacuum. There was obtained 6.6 g. of material boiling at 108° (0.1 mm.) $n^{24}D$ 1.5850.

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Notes

Derivatives of Morphine. III.[1] Sulfur Analogs of 14-Hydroxydihydrocodeinone

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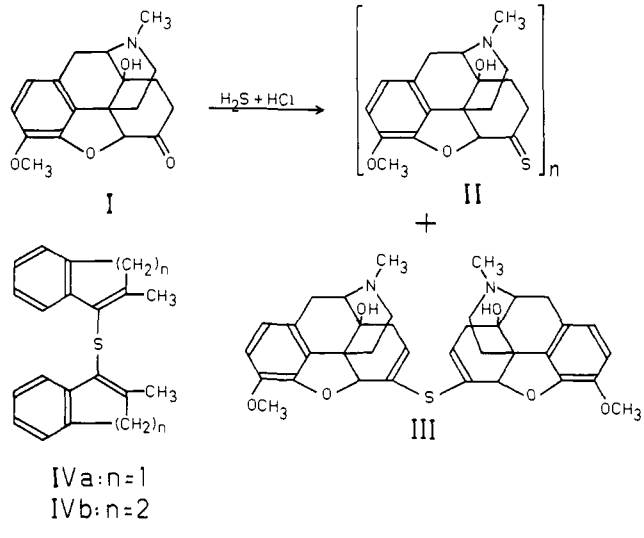
During the search for analgesic drugs with improved therapeutic properties, it appeared desirable to prepare some sulfur analogs of ketones of the morphine series. It has long been know that ketonic compounds of this series have a particularly strong analgesic action, and indeed the majority of those transformation products of morphine and codeine which have found use in therapeutic practice are ketones. It seemed, therefore, that corresponding sulfur compounds might be of interest. Because of its strong analgesic action, 14-hydroxydihydrocodeinone (I)[2] was chosen as the starting material.



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Treatment of I in cold chloroform with gaseous hydrogen sulfide and hydrogen chloride gave a mixture of two bases which could be separated by repeated extraction with boiling methanol. The methanol-insoluble fraction, on recrystallization from acetone, gave colorless crystals which did not melt below 300°. The method of preparation and the elemental analysis, the latter in excellent agreement with the formula $[C_{18}H_{21}NO_3S]_n$, suggest that II is the expected thioketone corresponding to I; it is undoubtedly present in the usual polymerized form.[3] While a few examples of dimeric thioketones are known,[4] trimer formation is the rule, so that n in the formula is assumed to be 3. The insolubility of the compound prevented experimental investigation of its molecular weight.

The second compound, present in the methanol-soluble fraction of the crude reaction product, was obtained pure by recrystallization from boiling methanol. It forms colorless leaflets melting at 231–233° to a pink liquid. The substance contains N and S in the ratio 2:1; it is thus undoubtedly sulfide III. Formation of compounds of this type (*e.g.*, IVa and b) has been studied by Campaigne and co-workers.[5] Elemental analysis of III is in satisfactory agreement with this formulation; while it does not with certainty exclude the possibility that III might be a sulfoxide rather than a sulfide, such an interpretation is unlikely because of the absence from the infrared spectrum of III of the characteristic intense sulfoxide band[6] at 1040 cm.$^{-1}$. Possibilities of acid-catalyzed O-demethylation or cleavage of the oxygen bridge, likewise not precluded by the elemental analysis, may be dismissed because of the lack of phenolic properties.

Pharmacological tests (hot plate method in mice)[7] indicate that III has a relatively weak analgesic action, significantly less than that of codeine. Compound II, on the other hand, is about comparable to codeine, with a similar time of onset but later peaking of effect and much longer duration of action. The prolonged action of II, if confirmed in man, might be of significance in the treatment of chronic pain. The comparative data are given in Table I.

TABLE I

ANALGESIC ACTIVITIES

	ED_{50}, mg./kg., s.c.	Onset, min.	Peak, min.	Duration, min.
Codeine	14.2	7.0	18	67
III	90.2	13.0	60	171
II	10.2	9.2	55	257
Morphine	2.1	13.0	34	129

Experimental

Microanalyses are by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Reaction of 14-Hydroxydihydrocodeinone with Hydrogen Sulfide and Hydrogen Chloride.—A solution of 9.1 g. of I in 400 ml. of chloroform was cooled to −10° and saturated with gaseous hydrogen chloride for about 30 min. Regardless of the formation of a white precipitate of the hydrochloride of I, streams of hydrogen chloride and hydrogen sulfide were passed simultaneously through the liquid for about 6 hr., while the temperature of the liquid was kept at about 0°. Excess hydrogen chloride and hydrogen sulfide were next removed by a stream of nitrogen, and the reaction mixture was extracted repeatedly with water. Addition of ammonia to the combined aqueous extracts precipitated a white amorphous mixture of bases. Extraction with chloroform yielded a greenish solution, part of the solid remaining undissolved. Evaporation of the filtered chloroform extracts *in vacuo* gave 7.0 g. of a white residue, which was boiled out repeatedly with methanol. The extracts were combined with the methanol solution of the original chloroform-insoluble solid, concentrated *in vacuo* to a small volume, and allowed to crystallize, yielding 1 g. of crude III. The methanol-insoluble portion of the crude bases, recrystallized from acetone, gave 6.4 g. of crude II.

Repeated recrystallization of the crude II from acetone or benzene gave the pure compound as colorless crystals which did not melt below 300° and decomposed on further heating.

Anal. Calcd. for $C_{18}H_{21}NO_3S$: N, 4.23; S, 9.68. Found: N, 4.14; S, 9.73; ratio N:S, 0.98.

Compound III, purified by several recrystallizations from boiling methanol, melted at 231–233° to a pink liquid. The product is insoluble in aqueous alkali and does not give any color with ferric chloride.

Anal. Calcd. for $C_{36}H_{42}N_2O_6S$: C, 68.76; H, 6.41; N, 4.46; O, 15.27; S, 5.09; mol. wt., 628.76. Found: C, 68.51; H, 6.00; N, 3.93; O, 16.3 (direct determination); S, 4.75; mol. wt. (Rast), 566; ratio N:S, 1.89.

Work on these compounds had to be terminated for external reasons before a detailed study of the most suitable procedures for their preparation and isolation had been carried out.

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4,4,6,16α-Tetramethyl-5-androstenes[1]

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Utilization of methyl iodide–potassium *t*-butoxide-*t*-butyl alcohol system for the conversion of Δ^4-3-keto steroids into 4,4-dimethyl-Δ^5-3-ketones[2] has been demonstrated, and recently Ringold and Malhotra[3] revealed the mechanism of such reaction.

Substitution at position 6 as well as 16 of steroids often results in significant enhancement of biological activities. It is, therefore, of considerable interest to investigate the effects of such substitutions of the 4,4-dimethyl-Δ^5-steroids.

Selective 4,4-dimethylation was carried out by promoting conjugated anion formation under Ringold

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