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Analgesics—III. Homologous Methadones

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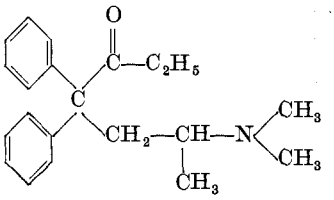
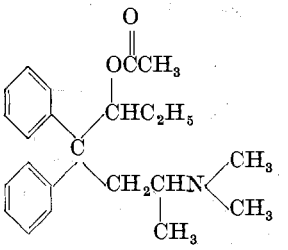
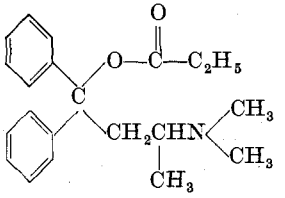
There has been some investigation of the changes in analgesia which accompany changes in the carbonyl location in methadone (I); *dl*-I[1] and *dl*-II[1] are approximately as active as morphine whereas (III) is reported to be 1/12 as active.[1]



(I)

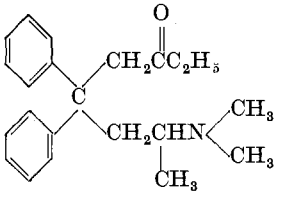


(II)

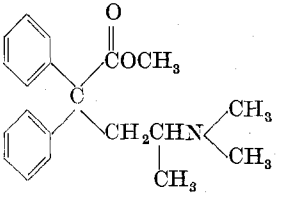


(III)

We became interested in the synthesis of (IV), which is the ketone analogue of (III), since (I) has considerably more activity than the ester (V).[1] Furthermore, (IV) is a stable structure



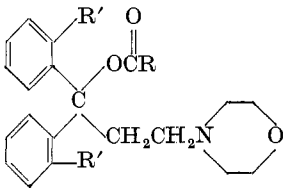
(IV)



(V)

whereas (III) undergoes solvolysis in water as a consequence of its tertiary benzhydryl ester structure.[2] Finally, structures of type (IV) present added latitude in comparison with (III) since reduction of the carbonyl and acetylation would lead to analogues whose relationships to one another might parallel those between (I) and (II).

It appeared advisable to have a *propyl*amine attached to the quaternary centre of (IV) since Beckett and Linnell[3] reported inactivity for a series of compounds (VIa, b, c) which are closely related to (III).

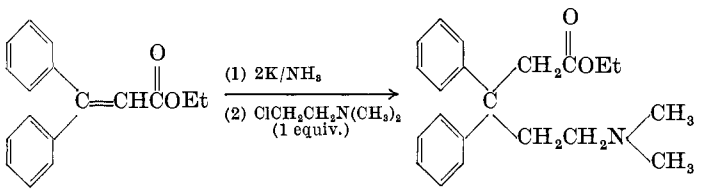


(VI)

a. R = CH_3—, R′
b. R = C_2H_5—, R′
c. R = C_3H_7—, R′

} = H or alkyl

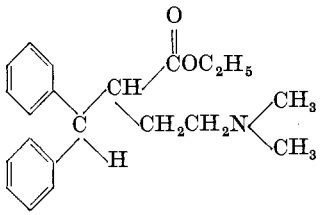
Turning to the synthesis of (IV), we first explored the β-alkylation of ethyl β,β-diphenylacrylate under conditions utilized by Hauser[4] for the β-alkylation of benzalacetophenone. The conditions for this type of reaction are summarized below:



(VIII)

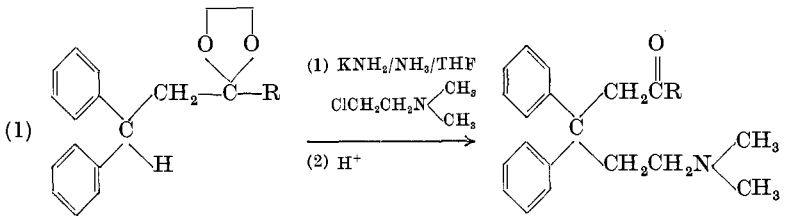
A hydrochloride was isolated in 30 per cent yield whose analysis and infrared spectrum were consistent with the desired product. The assignment of structure (VIII) is based on analogy with Hauser's results and on NMR evidence. A single sharp resonance (area = 2 protons) was observed in the region which is characteristic of protons adjacent to a carbonyl group. The isomeric structure (VIII, a) would be expected to have two resonances in the same general region each showing multiplet structure.*

* The authors wish to thank Dr. Nelson Trenner and Mr. Byron Arison for recording and interpreting this spectrum.



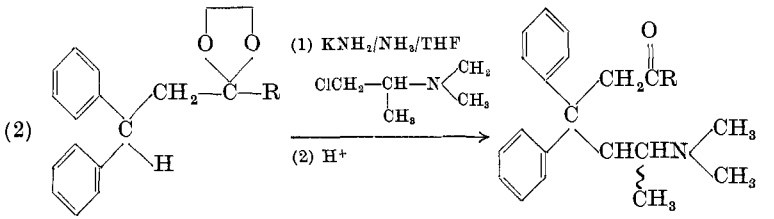
(VIII, a)

An attempt to conduct a similar alkylation with β-dimethylaminoisopropyl chloride gave a low yield of impure product. Development work might have been successful on this reaction but procedures for the conversion of the ester group to ketones would have to follow. These considerations prompted the exploration of a more direct route which is summarized below:



(IX)

a. R = CH_3—
b. R = C_2H_5—



(X)

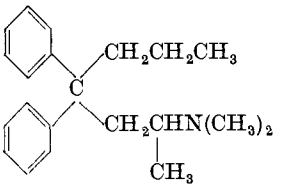
a. R = CH_3—
b. R = C_2H_5—

The syntheses of the diphenyl ketones and their dioxolanes were modelled on established procedures. No attempt was made to identify the methyl isomer which was isolated in the

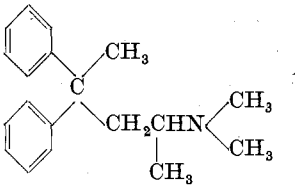
syntheses of (Xa) and (Xb), although the methadone-related isomer was probably formed in higher yield than the isomethadone derivative in parallel with the methadone synthesis itself.

All of the compounds in this series, (VIII), (IXa) and (IXb), and (Xa) and (Xb) were inactive as analgesics in the rat tail-flick test. It appears that —O— and —CH_2— are not interchangeable in (III).

A compound related to this series is (XI), which has a reported analgesic effect of very low order, and the corresponding methyl analogue (XII), which is 1/30–1/40 as potent as morphine.[5]



(XI)



(XII)

Experimental

Ethyl 5-dimethylamino-3,3-diphenyl-pentanoate. A 250-ml 3-neck round-bottom flask was flame dried and equipped with a Dry-Ice condenser, a magnetic stirrer and a KOH drying tube. Dry NH_3 (about 60 ml) was distilled in and then potassium (2·34 g) was added. Ethyl β,β-diphenylacrylate (7·6 g) in dry tetrahydrofuran (50 ml) was added with external cooling. A purple red colour developed which remained as most of the ammonia was distilled out through the KOH tube with the assistance of a warm water bath. The Dry-Ice condenser was replaced by a water condenser during this operation. β-Dimethylaminoethyl chloride (4·0 g) in dry tetrahydrofuran (25 ml) was added slowly with stirring to the reaction mixture at about 0°. After 15 min at this temperature, the stirred mixture was brought to a gentle reflux for 1 h. Then ammonium chloride solution was added carefully and the reactants were partitioned between dilute alkali and ether. The aqueous layer was further extracted with ethyl acetate and the combined solvents were washed and dried and the solvent distilled off. The product was dissolved in ether

and dry ice was passed into the solution to yield a gummy precipitate which was crystallized from acetone–ether. The yield was 3·4 g, m.p. 176–178°. An analytical sample, m.p. 182–183°, was prepared after several crystallizations from acetone–ethyl acetate.

Anal. Calcd. for $C_{21}H_{28}ClNO_2$: C, 69·69; H, 7·80. Found: C, 69·75; H, 7·81.

6-Dimethylamino-4,4-diphenyl-2-hexanone. 4,4-Diphenyl-2-butanone was prepared according to Burckhalter and Johnson[6] and converted to its dioxolane derivative by refluxing overnight the ketone (50 g), ethylene glycol (50 ml), *p*-toluenesulphonic acid (500 mg) and benzene (40 ml) in a Dean–Stark water separator. The reaction mixture was washed several times with 2N sodium carbonate, dried, and distilled from anhydrous potassium carbonate, b.p. 143–150°/1 mm. The derivative crystallized on standing. Carbonyl absorption was absent in the infrared.

A solution of KNH_2 from potassium (1·8 g) was prepared in dry NH_3(about 50 ml) containing a small amount of ferric chloride. When the blue colour had all disappeared, the above dioxolane (6·0 g) of 4,4-diphenyl-2-butanone was added slowly in dry tetrahydrofuran (25 ml). A bright red anion was formed. After 15 min of stirring under a Dry-Ice condenser, β-dimethylaminoethyl chloride (4·8 g) in dry tetrahydrofuran (25 ml) was added dropwise. After 15 min, the Dry-Ice condenser was replaced with a water condenser and the ammonia was boiled off through a KOH tube with the aid of slight warming. The reaction mixture was refluxed for 1 h, cooled, treated with water and extracted with ether. The basic products were extracted from the ether layer with 2·5N HCl and this solution was warmed on the steam bath for 10 min. The cooled solution was basified and extracted with ether. Precipitation of a hydrochloride was possible from this washed dried solvent. The yield of hydrochloride after one crystallization from methanol–ethyl acetate was 4·4 g, m.p. 244–246°.

Anal. Calcd. for $C_{20}H_{26}ClNO$: C, 72·38; H, 7·90; N, 4·22. Found: C, 72·10; H, 8·11; N, 4·46.

6-Dimethylamino-4,4-diphenyl-6 (or 5)-methyl-hexanone. This compound was prepared from the dioxolane of 4,4-diphenyl-2-butanone as above except that β-dimethylaminoisopropyl chloride was used in place of β-dimethylaminoethyl chloride.

The yield of crude basic product was 3·68 g from 45 g of the dioxolane. It was distilled, b.p. 145–149°/1·2 mm, and converted to its hydrochloride. After a number of crystallizations from acetone–ether and methyl ethyl ketone this salt had m.p. 202–205°. For analysis, a sample was reconverted to the free base, m.p. 98–100° from petroleum ether.

Anal. Calcd. for $C_{21}H_{27}NO$: C, 81·51; H, 8·80. Found: C, 81·58; H, 8·74.

1,1-Diphenyl-3-pentanone. 1-Phenyl-1-penten-3-one was prepared according to Harries and Müller.[7] It was reacted with benzene and aluminium chloride according to the procedure for 4,4-diphenyl-2-butanone.[5] The product was distilled, b.p. 140–144°/0·5 mm. A sample was recrystallized from petroleum ether, m.p. 37–38°. The NMR spectrum was in agreement with the assigned structure.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85·67; H, 7·61. Found: C, 85·68; H, 7·77.

An oxime was prepared, m.p. 119–122°, from ethanol. Kohler[8] describes fractional crystallization of the oximes of this ketone to yield the less soluble isomer as needles, m.p. 146°, and the more soluble one as lustrous plates, m.p. 117°.

7-Dimethylamino-5,5-diphenyl-3-heptanone. 1,1-Diphenyl-3-pentanone was converted to its dioxolane derivative and alkylated with β-dimethylaminoethyl chloride according to the procedure given above for 6-dimethylamino-4,4-diphenyl-2-hexanone.

The crude basic product was converted to its hydrochloride salt and recrystallized several times from methanol–ethyl acetate. The analytical sample had m.p. 186–187·5°.

Anal. Calcd. for $C_{21}H_{28}ClNO$: C, 72·91; H, 8·16. Found: C, 72·53; H, 8·00.

2-Dimethylamino-5,5-diphenyl-7(or 6)-methyl-3-heptanone. The dioxolane of 1,1-diphenyl-3-pentanone was alkylated with dimethylaminoisopropyl chloride according to the procedure for the preparation of 6-dimethylamino-4,4-diphenyl-6(or 5)-methyl-hexanone.

The crude basic product, 4·36 g from 50 g of the dioxolane, was distilled at 0·5 mm with a bath temperature of about 200°. The middle fraction was analysed as the free base.

Anal. Calcd. for $C_{22}H_{29}NO$: C, 81·69; H, 9·04. Found: C, 81·70; H, 8·92.

A perchlorate, m.p. 175–177°, was recrystallized from 2-propanol.

Anal. Calcd. for $C_{22}H_{30}ClNO_5$: C, 62·33; H, 7·13. Found C, 62·26; H, 7·37.

Summary. Several methadone analogues were prepared in which the ketone function was located *beta-* to the quaternary centre. They were devoid of analgesic activity.

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The pharmacology of these compounds was examined at the Merck Institute by Dr. Peter Orahovats and Mr. Edward Lehman. Their interest and assistance are gratefully acknowledged.

Microanalyses were under the supervision of Mr. R. N. Boos and the physical measurements were recorded by associates of Dr. Nelson Trenner.

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