TABLE II

Amine No.	Amine g	Cyanoguanidine, g	HCl, ml	H_2O, ml	EtOH, ml	Reaction time, min	Product No.	Yield g	Yield %	Mp, °C	Recrystn solvent
I	22.3	17.0	20.0	50		60	V[8,9]	25.0	57.5	258–260[a]	H_2O
II	4.0	0.9	1.2		3	60	VI[8,10,b]	1.0	57.0	183–184	Dil Me_2CO
III	11.6	9.2	9.2		50	45	VII	5.8	63.0	206–207	DMSO
IV	5.0	1.7	2.0	8		20	VIII	5.0	68.5	232–235	EtOH

[a] Dihydrochloride. [b] Code number T 1214.

from 5.0 mg/kg for VIII to 112 mg/kg for VI, XI, and XII (Table I).

Antimalarial Activity.[12]—Three compounds showed antimalarial activity: VI, X, and XII. Compound XII was the most active but showed a slight toxicity at the active doses, loss of weight at 160 mg/kg, LD_{80} = 320 mg/kg; VI was less active but no signs of toxicity were detected. The therapeutic dose is probably higher than 1000 mg/kg; X was less active but more toxic than VI; the results are collected in Table I.

Experimental Section

All analytical data of the new compounds were in agreement with the calculated ones for the expected structures. Ir absorption bands were also as expected. Biguanides V–VIII (Table II) were obtained as follows. The amines I–IV were mixed with HCl, solvent, and cyanoguanidine and refluxed; the resulting hydrochlorides were recrystallized (V) or converted into the bases (VI–VIII).

Amidinoureas IX–XII were obtained from biguanides on heating in dilute HCl (Table III).

TABLE III

Biguanide No.	Biguanide g	10% HCl, ml	Reaction time, min	Product No.	Yield g	Yield %	Mp, °C	Recrystn solvent
V	2.0	8	30	IX	1.5	75	246–247[a]	H_2O
VI	1.0	4	10	X	0.6	60	172–173	Dil Me_2CO
VII	2.5	5	15	XI	1.25	50	220–221[b]	EtOH
VIII	3.0	2.5	30	XII[c]	1.0	33	221–223	Dil pyridine

[a] Dihydrochloride. [b] Dihydrochloride monohydrate. [c] Code number T 1213.

Oxidation of VIII and XII.—To 3.3 g of VIII in 10 ml of AcOH, 8.0 g of 20% AcO_2H was added during 10 min; the temperature rose to 6 0–70°; after 2 hr the solvent was evaporated *in vacuo*, the mixture was made alkaline, and the resulting product was recrystallized from dilute Me_2CO yielding 2.7 g (75%) of VI, mp 183–184°. Similarly, 3.3 g of XII in 16 ml of AcOH gave 2.3 g (65%) of X, mp 172–173°.

Toxicity.[11]—Acute toxicity on oral administration was tested with Swiss male albino mice in groups of ten animals. The compounds were administered by stomach tube in a 5% suspension of aqueous gum arabic at 0.8 mg/20 g of body weight. The LD_{50} was calculated graphically according to Litchfield and Wilcoxon by the modification of Roth. The animals were observed for 10 days. Acute toxicity on intraperitoneal administration was investigated with compounds suspended in 4% Tween 80. The doses were 0.2 ml/20 g of body weight (Table I).

Antimalarial Activity.[12]—Tests were carried out using an old laboratory strain (strain N) of *Plasmodium berghei berghei*. Mice were inoculated intravenously with *ca.* 10^7 parasitized rbc on day 1. They were dosed orally with drugs in 10% (v/v) methylcellulose on days 1–4. Blood films were taken on fifth day. The percentage of red blood cells containing parasites was counted and compared with that of untreated control mice. Five mice were used for each dose. The relative parasitemia was calculated as a percentage of the controls (Table I).

(12) Tests were carried out at the National Institute for Medical Research, London.

Acknowledgments.—We wish to express our gratitude to Dr. L. J. Bruce-Chwatt and Dr. J. Haworth of the World Health Organization for their kind interest in our research and aiding us with supplies of instruments and materials. We are greatly indebted to Dr. F. Hawking, National Institute of Medical Research, London, for offering us facilities to carry the antimalarial tests, to Mrs. T. Bolesławska for assistance in the synthetic work, and to Mr. R. O. Folwell for help with antimalarial tests.

Catalytic Hydrogenolysis of Benzylmethylamino Analogs of Methadone and α-Methadol

A. F. CASY AND M. M. A. HASSAN

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta

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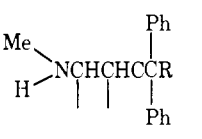
The great majority of analgetics with morphine-like effects are tertiary amines.[1,2] Among the few examples of active secondary amines that have been reported are the N-methylamino analogs of methadol and acetylmethadol,[3] normorphine,[2] and certain 6,-14-endoethenotetrahydrothebaines.[4] Interest in analgetics with secondary amino functions has been aroused as a result of a hypothesis implicating such bases as intermediates in the mediation of analgesia.[2,5]

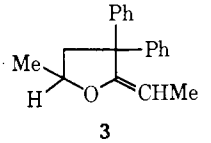
3-Methylamino-1,1-diphenylpropylamines (**1**) (R is an oxygenated function) have proved difficult to synthesize from corresponding N-dimethylamino analogs. Thus, treatment of methadone (**2a**) and α-methadol (**2b**) with BrCN yields the cyclic products **3** and **4**, respectively, rather than the N-cyanomethyl derivatives, potentially capable of hydrolysis to the



1

$Me_2NCHMeCH_2CPh_2R$

2a, R = COEt
b, R = CHOHEt
c, R = CH(OCOMe)Et



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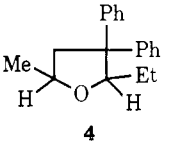

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(2) A. H. Beckett and A. F. Casy, *Progr. Med. Chem.*, **2**, 43 (1962); **4**, 171 (1965).
(3) N. B. Eddy, *Chem. Ind.* (London), 1462 (1959).
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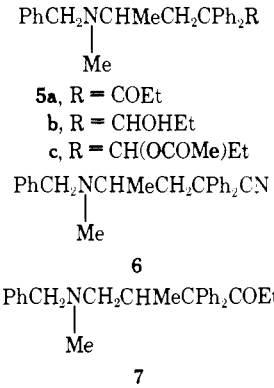
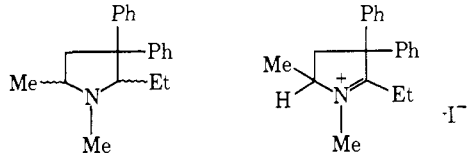
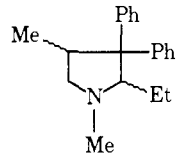
desired secondary amines.[6,7] The N-methylamino derivative of α-acetylmethadol (**2c**) has, however, been reported in the patent literature,[8] being prepared by catalytic hydrogenolysis of the N-benzylmethyl amino analog **5c**. In a further investigation of this route the



N-benzylmethylamino ethyl ketone **5a** (prepared from the cyanide **6**) was subjected to catalytic hydrogenolysis in the expectation of obtaining the N-methylamino analogs of methadone and/or α-methadol. Formation of the methadol **11b** was indicated initially because 2 moles of H_2 were absorbed in the reaction. The product, however, was proved to be the pyrrolidine derivative **8** from ir (absence of ν_{OH} and ν_{NH} bands in the spectrum of the base) and pmr characteristics [the N–Me pmr signal was a singlet in the base and a doublet (J = 5 Hz) in the salt (solvent, $CDCl_3$) rather than the doublet (base) and triplet (salt) expected for **11b**, while the *sec*-Me–Et signal was complex and did not resemble that of acyclic methadols] and from microanalytical data. In further confirmation, a sample of **8** prepared unambiguously by reduction of the Δ′-pyrroline **9**[9,10] was identical with the product derived from **5a**. Debenzylation of the isomeric ketone **7** similarly gave a cyclic product **10**; this proved

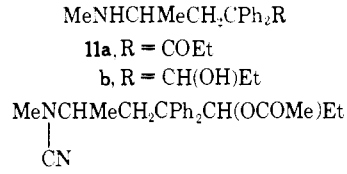




more difficult to characterize because a solid base could not be obtained and the HCl salt crystallized with 1 mole of water. Its identity was established, however, through ir (absence of ν_{OH} and ν_{NH} in free base) and pmr characteristics, failure to display alcoholic properties (no O-acetyl derivative and resistance to elimination conditions), and by the probable identification of a cyclic reaction intermediate (see below). The configurations of **8** and **10** are unknown.

There are two probable pathways for the conversion of **5a** to **8**: (1)] formation of the noralcohol **11b** followed by loss of water and concomitant cyclization, or (2) formation of the norketone **11a** followed by its cyclization to the Δ′-pyrroline **9** which is then reduced to **8**.

If the first pathway is correct, debenzylation of the amino alcohol **5b** (obtained by treating **5a** with LAH) should give the same cyclic product. In fact, this alcohol was converted to the secondary base **11b**, characterized by ir (presence of ν_{OH} and ν_{NH} bands in the free base and HCl salt spectra) and pmr characteristics [the N–Me signal of the salt in $CDCl_3$ was a triplet (J = 5 Hz, collapsing to a singlet when D_2O was added) indicative of an H_2N^+Me group (the base N–Me signal could not be resolved) while the *sec*-Me–Et signal was characteristic of acyclic methadols] and by microanalytical results. An identical product was isolated upon acid hydrolysis of the N-cyanomethyl analog **12** of α-acetylmethadol. The *sec*-amino alcohol



11b is mentioned in the patent in ref 8 but without evidence of structure.

Evidence for the second mechanism was provided from an experiment in which the catalytic hydrogenation of the benzylmethylamino ketone **7** was interrupted after the uptake of 1 mole of H_2. Unreacted ketone was recovered together with a basic oil which had an ir spectrum characteristic of the Δ′-pyrroline **9**, in particular, a strong band at 1650 cm^{-1} assigned to C=N stretching. It rapidly developed a red color, behavior also characteristic of **9**.

The saturated cyclic product **8** lacked significant analgetic properties as established by its high ED_{50} value (56 mg/kg) in the mice hot-plate test. Thanks are due to Dr. Everette L. May of the National Institutes of Health, Bethesda, Md., for arranging this test.

The cyclic product **9** has been shown to be a major metabolite of methadone in rats and in man,[10] and it almost certainly results from the N-demethylated ketone **11a**. N-Demethylation of methadol and its acetate is equally likely but unchanged nor products rather than cyclized forms are probably metabolites in these cases since this work has established the stability of diphenylpropylamines with secondary amino and hydroxyl functions. Metabolites of this nature may well play a role in the mediation of the analgetic effects of the parent dimethylamino compounds (*cf.* ref 11) in view of their significant analgetic properties.

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Experimental Section

When analyses are indicated, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Catalytic Hydrogenation of 6-Benzylmethylamino-4,4-diphenylheptan-3-one and Its 5-Methylhexan-3-one Isomer.—A mixture of the amino ketone **5a**[12] (20 g), 4 *N* HCl (20 ml), 10% Pd–C (2.5 g), and EtOH (400 ml) was shaken with H_2 at room temperature and pressure until gas uptake ceased. The filtered product was evaporated and the residual salt (11 g) gave the **pyrrolidine base 8**: bp 128–132° (0.5 mm) (8 g); mp 56–58° from EtOH; N–Me pmr characteristics in $CDCl_3$ (Hz from TMS), base 147 (singlet), HCl 176 (doublet J = 5 Hz). *Anal.* ($C_{20}H_{25}N$) C, H, N.

The same product, mp and mmp 56–58°, was obtained by shaking a mixture of the freshly distilled base (2.5 g) from 2-ethyl-4-methyl-3,3-diphenyl-Δ′-pyrroline hydriodide **9**,[9,10] 10% Pd–C (0.2 g), and EtOH (70 ml) with H_2 at 60°. The hydriodide **9** resisted hydrogenation under these conditions. The same reduction procedure applied to the benzylmethylamino ketone **7**[12] gave the 4-methylpyrrolidine isomer **10** as a **hydrochloride monohydrate**, mp 226–227° from EtOH–Et_2O. *Anal.* ($C_{20}C_{26}ClN\cdot H_2O$) C, H, N.

Debenzylation of 6-Benzylmethylamino-4,4-diphenylheptan-3-ol.—The benzylmethylaminomethadol **5b** (α isomer) was obtained as a hydrochloride, mp 188–190° (lit.[8] 178–179°) from EtCO–Et_2O, by treating the ketone **5a** with LAH. *Anal.* ($C_{27}H_{34}ClNO$) C, H, N. A mixture of the free base **5b** (6 g), 4 *N* HCl (6 ml), 10% Pd–C (1 g), and EtOH (120 ml) was shaken with H_2 and processed as described for the reduction of **5a**. The *sec*-amine reaction product **11b** was isolated as a **hydrochloride** (3 g): mp 183–185° from EtOH–Et_2O; N-Me pmr characteristics of HCl (Hz from TMS), 135 (triplet J = 5) in DMSO-d_6, 145 (triplet J = 5) in $CDCl_3$. The salt had a sharp ir absorption at 3400 cm^{-1} (ν_{OH}) and the base at 3280 cm^{-1} superimposed upon a broad shoulder between 3500 and 3100 cm^{-1} typical of methadols (ν_{OH} and ν_{NH}). *Anal.* ($C_{20}H_{28}ClNO$) C, H, N.

Hydrolysis of α-3-Acetoxy-6-cyanomethylamino-4,4-diphenylheptane.—A mixture of the N-cyanomethyl derivative **12** (15 g)[7] and 6% HCl in H_2O (300 ml) was heated under reflux for 12 hr, cooled, and extracted (Et_2O) to remove nonbasic products. The base (3.5 g) recovered from the aqueous phase as usual was treated with HBr–EtOH to give the ***sec*-amine 11b hydrobromide,** mp 206–207° from EtOH–Et_2O. *Anal.* ($C_{20}H_{28}BrNO$) C, H, N. The melting point of this salt was undepressed by the hydrobromide of the *sec*-amine derived from **5b**.

Pmr spectra were recorded on a Varian A-60 spectrometer with $CDCl_3$ or DMSO-d_6 as solvents and TMS as standard.

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Synthesis of Some Ureidodihydrofurans and Related Pyrimidones as Potential Antimalarials[1,2]

E. CAMPAIGNE, R. L. ELLIS, M. BRADFORD, AND J. HO

Chemistry Laboratories of Indiana University, Bloomington, Indiana 47401

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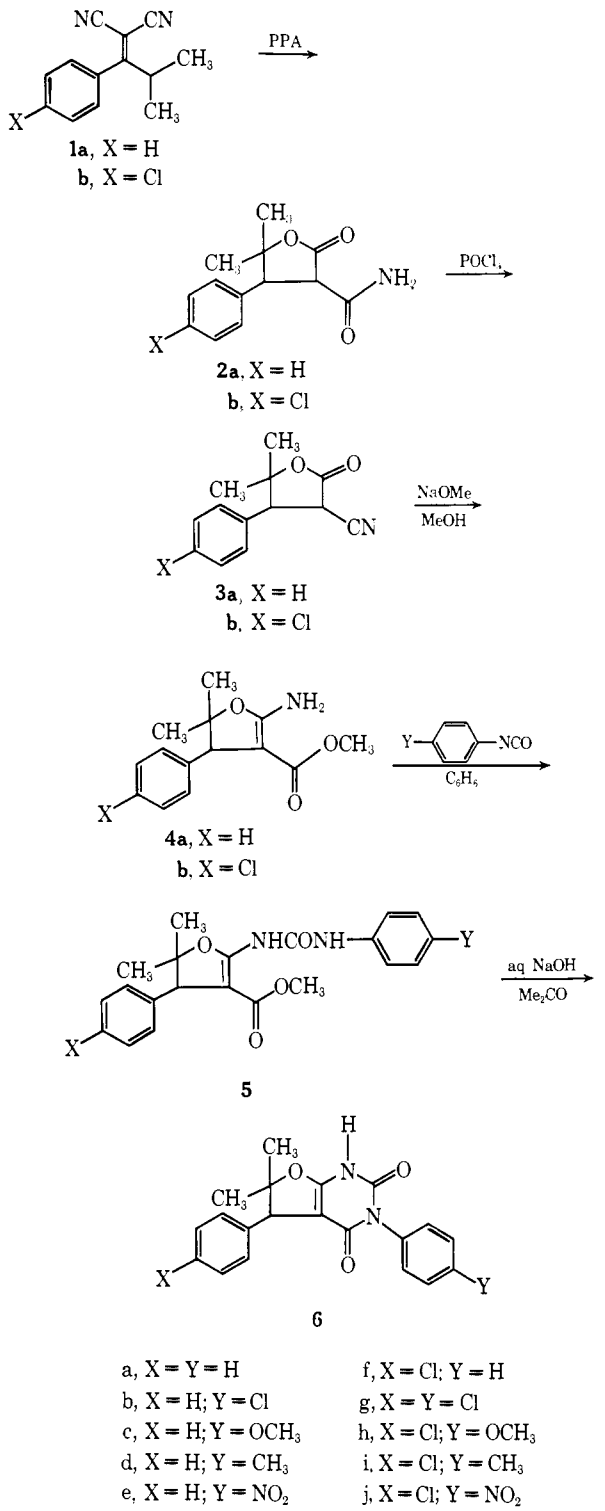
Extensive studies have been carried out in these laboratories concerning sulfuric acid cyclizations of ylidenemalonitriles derived from aryl- and alkyl-substituted aromatic ketones[3–6] leading to the formation of both indenone and indanone derivatives. Cyclization, however, of certain alkyl-substituted ylidenemalononitriles in polyphosphoric acid (PPA) leads to the formation of butyrolactones[7,8] which contain functional groups susceptible to metathesis. For example, cyclization of α-cyano-β-isopropylcinnamonitrile (**1a**) in hot PPA produces the lactone **2a** (see Chart I). It was envisioned that **2a** offered

CHART I



a, X = Y = H	f, X = Cl; Y = H
b, X = H; Y = Cl	g, X = Y = Cl
c, X = H; Y = OCH_3	h, X = Cl; Y = OCH_3
d, X = H; Y = CH_3	i, X = Cl; Y = CH_3
e, X = H; Y = NO_2	j, X = Cl; Y = NO_2

(1) Contribution No. 1640 from the Chemistry Laboratories of Indiana University.

(2) Taken in part from the thesis of R. L. E. submitted to the Graduate School of Indiana University in partial fulfillment of the requirements for the Ph.D. degree, May 1967.

(3) E. Campaigne and G. F. Bulbenko, *J. Org. Chem.*, **26**, 4703 (1961).

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(5) E. Campaigne, D. R. Maulding, and W. L. Roelofs, *ibid.*, **29**, 1543 (1964).

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(7) E. Campaigne and R. L. Ellis, *Chem. Commun.*, 141 (1966).

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