with carbonyls in the 3, 7, and 12 positions required 3 hr. at 50–55° for quantitative reactivity. Prednisone, a 3,11,20-trione compound, gave 66.7% recovery after 3 hr. and no further reaction was evident after 17 hr. elapsed time. Since the 11 keto position is known to be extremely unreactive, the result at 3 hr. can be considered quantitative based on hydrazone formation at the 3 and 20 positions only. Progesterone, prednisolone, and methylprednisolone which represent 3,20 di-ketones yielded quantitative bis-hydrazones. Prednisolone, esterified as the acetate, gave an incomplete reaction—81.5%—after 3 hr. The presence of the bulkier substituent adjacent to carbon 20 appears to be sufficient to drastically hinder the formation of hydrazone at the C_{20} carbonyl.

SUMMARY

The titration of excess 2,4-dinitrophenylhydrazine using sodium nitrite without prior separation of the precipitated hydrazone allows a shorter analysis time for the determination of aldehydes and a substantial number of ketones. The procedure was found to be reproducible to ±0.5% and the results for ethyl vanillin, formaldehyde solution U.S.P., prednisolone, menadione, and prednisone were consistently within 0.5% of comparative values obtained by official or other recognized methods of analysis.

The method is neither applicable to certain aliphatic ketones nor to sterically hindered steroids. Carbonyl compounds which contain a functional group such as an amine or phenol capable of reacting with sodium nitrite cannot be determined by the proposed procedure.

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Amides Derived from Hepta- and Octamethyleneimine

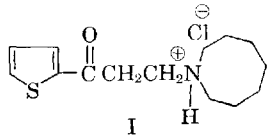
By HEINO A. LUTS, W. A. ZUCARELLO*, W. LEWIS NOBLES†, and JEROME F. GRATTAN

Some new physiologically active amides of hepta- and octamethyleneimine moiety have been prepared. Their preparation and biological activities are given.

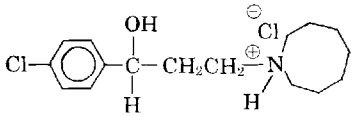
THE KNOWLEDGE that a number of biologically important compounds occurring in nature contain trimethoxyphenyl or trimethoxybenzoyl groups as a part of their molecule has prompted considerable investigation into the various ways which this moiety can be incorporated into molecules and elicit various pharmacological actions.

Vargha and his associates (1) have reported on the tranquilizing and analgesic effects of the simple benzamide containing the above moiety as well as a number of heterocyclic amides. In varying the amine moiety of the amide, they noted that morpholine and 2-methylmorpholine exhibited the most desirable therapeutic properties among the compounds studied. Correspondingly, Schlager (2) in a review article has reported on a large number of derivatives containing 3,4,5-trimethoxybenzoyl moiety.

Previously, the authors (3) have reported on the use of heptamethyleneimine in the Mannich reaction. It may be worthy of note that in this earlier work, the Mannich base obtained from 2-acetylthiophene and heptamethyleneimine exhibited significant analgesic activity at a dosage level of 150 mg./Kg.



I



II

In addition, the secondary alcohol obtained by the sodium borohydride reduction of the Mannich base from *p*-chloroacetophenone and heptamethyleneimine

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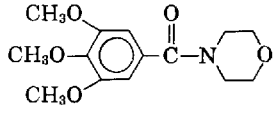
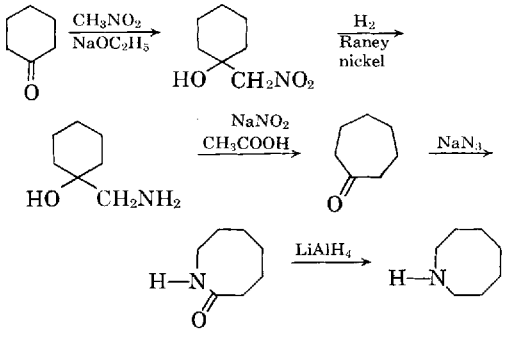
exhibited marked analgesic activity at a dosage level of 32 mg./Kg.

In addition to the work of Vargha and associates (1), the pharmacological activities of a number of different amides have been observed; these have exhibited sedative, analgetic, anticonvulsant, and cardiotonic activity (4). It is perhaps particularly noteworthy that *N*-3,4,5-trimethoxybenzoylmorpholine has elicited marked neurodepressive as well as analgetic activity (5, 6).



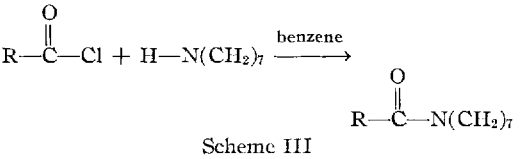
III

It is apparent in a review of the literature that the heterocyclic amine moiety has not been studied in molecules possessing seven to eight methylene groups



Scheme I

as an integral part of the structure. Hence, a concerted literature review was carried out as a prelude to the extension of the authors' studies to rings larger than pyrrolidine and piperidine, *i.e.*, heptamethyleneimine and octamethyleneimine. It was anticipated that the enlargement of the carbon



Scheme III

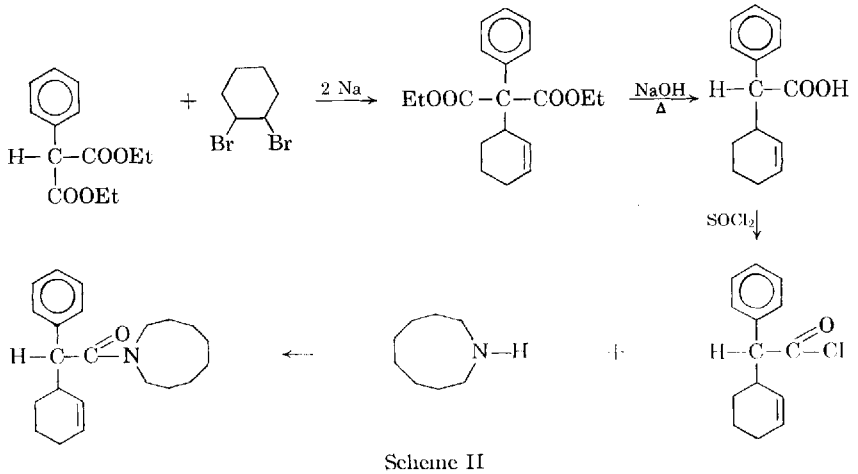
content of the amine moiety would increase the lipid solubility, and perhaps differ in enzymatic attack.

With the increasing availability of furan derivatives, considerable interest has been evidenced in the preparation of furan relatives of compounds of the benzene series which possess medicinal value; the same is true of a great number of pyridine derivatives. Thus, also drawing from previous knowledge of the activity of *N*-3,4,5-trimethoxybenzoylmorpholine, the hepta- and octamethyleneimine amides of this same acid moiety have been prepared and submitted for pharmacological study. In addition, certain heterocyclic acids have been condensed with these same amines. Furthermore, α-phenyl, α-cyclohexenyl acetic acid was utilized as an acid moiety because of the widespread use of acids of this general type in antispasmodics.

The method of preparing cyclohepta- and cyclooctanones was that of Boeseken and Derx (7); for hepta- and octamethyleneimine, the method was that of Blicke and Doorenbos (8) (Scheme I). The α-phenyl, α-cyclohexene acetic acid was by the Neesby *et al.* (9) (Scheme II) method. All the acid chlorides were prepared by the standard method of using thionyl chloride. The amides were prepared by reacting acid chlorides with heptamethyleneimine in benzene (Scheme III).

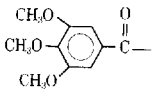
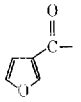
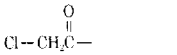
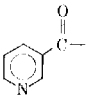
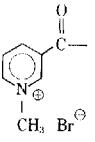
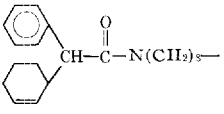
EXPERIMENTAL

General Procedure.—To a solution of 0.05 mole of appropriate acid chloride in 150 ml. of benzene solution was added dropwise 0.1 mole of appropriate amine. The reactants were then refluxed for 30 min. and formed crystals, separated by filtration. The benzene solution was then evaporated to dryness and the formed crystalline product washed twice with petrolcum ether.



Scheme II

TABLE I.—ANALYTICAL RESULTS
R—N(CH$_2$)$_7$

Compd.	R	Over-All Yield	Mol. Wt.	M.p., °C.	Formula	Anal., N Calcd.	Anal., N Found
I		78	307.37	86	$C_{17}H_{25}NO_4$	4.56	4.46
II		89	207.25	(b.p.) 141–149/ .3–.35 mm.	$C_{12}H_{17}NO_2$	6.76	6.81
III		84	189.66	62–63	$C_9H_{16}ClNO$	7.37	7.28
IV		82	218.28	(b.p.) 162–170/ .24 mm.	$C_{13}H_{18}N_2O$	12.83	12.98
V		94	313.22	173	$C_{14}H_{21}BrN_2O$	8.95 Br = 25.89	9.04 Br = 26.51
VI		87	325.47	100–101	$C_{22}H_{31}NO$	4.28	4.53

PHARMACOLOGICAL DATA

The preliminary pharmacological findings demonstrate that compound I (Table I) is a mild stimulant, and not a depressant, with a poor over-all activity. No analgesic activity was found. Compound II exhibited depressant effect; following a brief period of mild excitation, it also exhibited anticonvulsant activity and at a low dose level. Furthermore, compound II antagonized strychnine and exerted a weak analgesic effect and had local anesthetic effect at the 1% dose level when instilled repeatedly in rabbit's eye. Compound III also exhibited depressant activity and was a spasmolytic agent. It antagonized the tremors consequent on tremorine injection, although it did not antagonize the parasympathomimetic effects of the drug. Furthermore, it also exerted a mydriatic effect. Compound IV acted as a stimulant; no reserpine antagonism, but compound V was a mild depressant. Both compounds were cholinergic and peripheral vasodilators. Compound VI has shown some antispasmodic activity; the compound is still under investigation. A more detailed report will be presented in another publication.

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