Anal. Calcd for $C_{25}H_{23}NO_9$: C, 62.36; H, 4.95; N, 2.91; mol wt, 481. Found: C, 62.40; H, 5.08; N, 2.82.

Condensation of Oxazolone 6 with Dimethyl 3-Oxoglutarate.—In a manner identical with that described for the reaction of oxazolone **5**, 878 mg (2.74 mmol) of **6** was allowed to react with 570 mg (3.28 mmol) of dimethyl 3-oxoglutarate and 75.5 mg (3.15 mmol) of sodium hydride. A yield of 1.27 g of a yellow oil was obtained which, upon addition of methanol–ether, gave 746 mg (55% of theory) of **10**: mp 140–144°. An analytical sample was obtained from methanol–ether: λ_{max}^{KBr} 2.9, 5.7, 5.75, 5.95, and 6.2 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 254 (23,000), and 227 (19,800); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 254 (24,900) and sh 227 (19,450); nmr ($CDCl_3$), δ 1.15 (t, J = 7 cps, 3 H, –O–CH_2–**CH_3**), 4.1 (q, J = 7 cps, 2 H, O–**CH_2**–CH_3), 3.52 (s, 3 H, methyl ester), 3.93 (3 H methyl ester), 3.76 (s, 1 H, methine), 4.70 (s, 1 H, benzylic methine), and 7.2–7.9 (m, 11 H, aromatic and N–H).

Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.08; N, 2.82; mol wt, 495.5. Found: C, 63.13; H, 5.02; N, 2.74.

Condensation of Oxazolone 7 with Dimethyl 3-Oxoglutarate.—A 622-mg (1.7 mmol) sample of **7**, 355 mg (2.04 mmol) of dimethyl 3-oxoglutarate, and 46.5 mg (1.95 mmol) of sodium hydride were dissolved in 10 ml of tetrahydrofuran. After 3.5 days at room temperature the mixture was worked up in the usual fashion and gave 584 mg of a yellow oil. A yield of 308 mg (34% of theory) of a white solid (**11**) was obtained after crystallization from methanol–ether: mp 150–158°; λ_{max}^{KBr} 2.9, 5.7, 5.8, 6.0, 6.25, and 9.7 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 250 (24,570) and sh 290 (4700); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 251 (26,180) and sh 290 (5850); nmr ($CDCl_3$), δ 1.11 (t, J = 7 cps, 3 H, O–CH_2–**CH_3**), 4.1 (q, J = 7 cps, 2 H, O–**CH_2**–CH_3), 3.57 (s, 3 H, methyl ester), 3.95 (s, 3 H, methyl ester), 3.77 (s, 1 H, methine), 4.67 (s, 1 H, benzylic methine), 5.99 (s, 2 H, methylenedioxy), and 6.7–8.0 (m, 10 H, aromatic and N–H).

Anal. Calcd for $C_{27}H_{25}NO_{11}$: C, 60.11; H, 4.67; N, 2.59; mol wt, 539.5. Found: C, 60.03; H, 4.81; N, 2.54.

Hydrolysis and Decarboxylation of 9.—To a solution of 500 mg (1.04 mmol) of **9** in 10 ml of hot methanol, 100 ml of a 5% barium hydroxide solution in water was added. The mixture was heated on a steam bath for 2 hr. During this time a white precipitate formed from the initially colorless, homogeneous solution. The mixture was then acidified with 1 *N* HCl and heated for an additional 10 min. During this time the acid **12** crystallized. After cooling, 270 mg (74%) of **12** was collected, mp 261°. An analytical sample was recrystallized from methanol–ether: λ_{max}^{KBr} 3.0, 2.7–4.4 (broad), 5.9, 6.15, and 6.22 μ; λ_{max}^{MeOH}, mμ (ϵ), 249 (17,550) and 225 (17,550); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ) 268 (21,500) and 225 (15,780).

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.98; mol wt, 351.4. Found: C, 68.37; H, 4.93; N, 3.93.

Preparation of the Ester Enol Ether 15 from 12.—To a cold solution of 130 mg (0.356 mmol) of **12** in 10 ml of ether was added a solution of diazomethane (0.80 mmol). Another portion of diazomethane was added after 4 hr and the mixture stirred at room temperature for 18 hr. The solvent was removed *in vacuo* and a sample of the recovered foam exhibited no bathochromic shift in alkaline methanol. A sample was crystallized from ether, mp 142–144°. Recrystallization of **15** from methanol–ether gave a 1:1 methanol adduct: mp 83–85°; λ_{max}^{KBr} 3.0, 5.8, 5.92, 6.05, and 6.3 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 243 (20,850) and sh 225 (18,900); $\lambda_{max}^{0.01\ N\ methanol\text{-}NaOH}$, m$\mu$ (ϵ), 243 (20,850) and sh 225 (18,900); nmr ($CDCl_3$), δ 3.22 (AB, J = 17 cps, 2 H, methylene), 3.75 (s, 6 H, enol ether and methyl ester), 4.02 (s, 1 H, benzylic methine), 5.23 (s, 1 H, vinyl), and 7.2–8.0 (m, 11 H, aromatic and N–H).

Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.95; H, 5.58; N, 3.69; mol wt, 379.4. Found: C, 69.89; H, 5.48; N, 3.72.

Preparation of the Acid Enol Ether 14.—A 378-mg (1.08 mmol) portion of **12** and 10 mg of *p*-toluenesulfonic acid was dissolved in 75 ml of benzene and 50 ml of methanol and distilled over 5 hr to a volume of 30 ml. The solution was diluted with ether and washed with dilute alkali. The organic phase was dried over sodium sulfate and evaporated to dryness under reduced pressure to give 41 mg (8% of theory) of the ester enol ether **15**, mp 140–144°. The alkaline solution was then acidified and washed with chloroform. The combined organic extracts were washed with water, dried over sodium sulfate, and evaporated to give 446 mg (62% of theory) of **14**: mp 125–128°; λ_{max}^{KBr} 2.95, 2.7–4.4 (broad), 5.85, 6.0, 6.3, and 7.35 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 243 (19,050) and sh 228 (18,050); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 228 (19,650) and sh 240 (18,900); nmr (D_2O–NaOD), δ 3.0 (d AB pattern, 2 H, methylene), 3.30 (s, 3 H, enol ether), 3.58 (s, 1 H, methine), 4.8 (s, HOD), 5.18 (s, 1 H, vinyl), and 7.0–8.0 (m, 10 H, aromatic).

Anal. Calcd for $C_{21}H_{19}NO_5 \cdot CH_3OH$: C, 66.48; H, 5.83; N, 3.54; mol wt, 402. Found: C, 66.71; H, 5.54; N, 3.61.

Preparation of the Ester Enol Ether 15 from 14.—To a suspension of 590 mg (1.61 mmol) of the acid enol ether **14** in 10 ml of cold ether was added a solution of diazomethane (4.8 mmol). Immediately upon addition of the diazomethane the solution became homogeneous. After 30 min a white solid crystallized from the cold solution. Stirring was continued for 12 hr and the excess diazomethane was removed by warming the solution slightly under reduced pressure. A 550-mg (86%) portion of the ester enol ether **15** was collected and shown to be identical with that prepared directly from **12**.

Registry No.—**5**, 15924-08-0; **6**, 15924-09-1; **7**, 15963-73-2; **9**, 15924-10-4; **10**, 15924-11-5; **11**, 15924-12-6; **12**, 15924-13-7; **14**, 15924-14-8; **15**, 15924-15-9.

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Preparation of Tertiary N,N-Dimethylamines by the Leuckart Reaction

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Introduction of alkyl groups into ammonia or a primary or secondary amine by means of certain aldehydes or ketones, when the reducing agent is ammonium formate, is known as the Leuckart reaction.[2,3] Later, Wallach[4] obtained better yields by using a mixture of ammonia or substituted amine with formic acid. The Leuckart reaction did not come into general use as a preparative method until 1936 when Ingersoll and coworkers[5] reviewed the subject and applied the reaction to the synthesis of a series of substituted β-phenylethylamines. Similarly, Novelli[6] showed that respectable yields of secondary amines could be obtained by the action of N-alkylformamides on some substituted acetophenones. When the carbonyl compound is formaldehyde, the transformation is termed the Clarke–Eschweiler[3] method.

The Leuckart reaction applied to the synthesis of tertiary amines has found only limited application to date. Early examples of the reaction where an aldehyde or ketone has been treated with a dialkylformamide include the reaction of benzaldehyde with formylpiperidine to give N-benzylpiperidine,[4] and the conversion

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TABLE I
TERTIARY AMINES SYNTHESIZED[a]

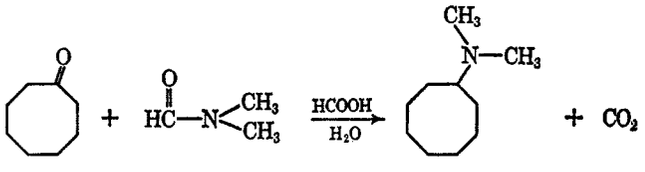
Ketone	Tertiary amine product	% yield of amine	% yield of methiodide	Picrate mp, °C
Cyclopentanone	N,N-Dimethylcyclopentylamine	61		176.5–178[b]
Cyclohexanone	N,N-Dimethylcyclohexylamine	70	61[m]	178.5–179.5[c]
Cycloheptanone	N,N-Dimethylcycloheptylamine	55	71	186–187[d]
Cyclooctanone	N,N-Dimethylcyclooctylamine[f]	75		197–198[e]
Cyclodecanone	N,N-Dimethylcyclodecylamine	76		145–146[g]
2-Octanone	N,N-1-Trimethylheptylamine	65		59.5–61.5[h]
Acetophenone	N,N,α-Trimethylbenzylamine	58		138–139[i]
3-Pentanone	N,N-Dimethyl-1-ethylpropylamine	38		180.5–181.5[j]
Norcamphor	*endo*-2-Dimethylaminonorbornane[k]	70		220–222[l]

[a] See Experimental Section for procedure. [b] Lit.[10] 177–178°. [c] Lit.[10] 175–176°. [d] M. Mousseron, R. Jacquier, and H. Christol [*Compt. Rend.*, **235**, 57 (1952)] reported mp 184°. [e] C. G. Overberger, M. A. Klotz, and H. Mark [*J. Amer. Chem. Soc.*, **75**, 3186 (1953)] reported mp 195.8–197.4°. [f] Submitted for publication in *Org. Syn.* [g] A. C. Cope, R. J. Cotter, and G. G. Roller [*J. Amer. Chem. Soc.*, **77**, 3590 (1955)] reported mp 145.8–147.4°. [h] *Anal.* Calcd for $C_{16}H_{26}N_4O_7$: C, 49.73; H, 6.78; N, 14.50. Found: C, 49.57; H, 6.95; N, 14.83. This compound was recrystallized twice from ethanol. All other melting points are reported after one recrystallization from ethanol. [i] G. Wittig, R. Mangold, and G. Felletschin [*Ann.*, **560**, 116 (1948)] reported mp 137–138°. [j] A. C. Cope, N. A. LeBel, H. H. Lee, and W. R. Moore [*J. Amer. Chem. Soc.*, **79**, 4720 (1957)] reported mp 180.5–182.5°. [k] The product is believed to be almost entirely the *endo* isomer. The *endo*-amine has a strong band in the infrared at 795 cm^{-1} which is absent in the spectrum of the *exo* isomer. Furthermore, the *exo* isomer has a strong band at 1022 cm^{-1} and a medium band at 820 cm^{-1}, both of which are absent in the spectrum of the *endo* isomer (see ref 17). [l] Reported 218–220° for the *endo* isomer; see ref 17. [m] The crude N,N-dimethylcyclohexylamine was converted into its methiodide without purification (see Experimental Section) and had mp 280–281° dec. A. Skita and H. Rolfes [*Ber.*, **53**, 1242 (1920)] reported mp 277°.

of furfural into N,N-dimethylfurfurylamine.[3,7,8] Subsequently, Bunnett and Marks[9] prepared six tertiary amines from ketones and dialkylformamides and obtained yields ranging from 21 to 54%. However, they found that the reactions failed to give tertiary amines in the absence of magnesium chloride catalysis.

An all encompassing mechanism for the Leuckart reaction has not been reported. Mousseron[10] has studied the action of formamide and N-mono- and N,N-dialkylformamides on cyclopentanones and cyclohexanones in an effort to establish the mechanism of this reaction. As a result of a deuterium-labeling study, Rekashera and Miklukhin[11] have argued against the mechanism proposed by Mousseron. In contradiction to the common opinion on the ionic mechanism[3,10,11] postulated for the Leuckart reaction, Lukasiewicz[12] has suggested that this reaction and the reduction of imines by formic acid take place according to a free-radical mechanism.

Our initial efforts in this area were directed toward the synthesis of N,N-dimethylcyclooctylamine which heretofore had been prepared by a number of less direct routes.[10,13–15] When cyclooctanone was treated with dimethylformamide and formic acid in an autoclave at 190°, the desired amine was obtained in good yield (75%). The crude product, isolated after acid and then base extraction, was pure to vpc and could be used without distillation in subsequent reactions (see the Experimental Section for details). The only by-product isolated from the reaction was cyclooctanol (10%), in addition to recovered cyclooctanone (10%). Optimum yields were obtained in the temperature range of 175–190°. Lowering the temperature to 160° reduced the yield of tertiary amine, although at the lower temperature very little reduction to cyclooctanol occurred. Reaction times of 8–16 hr were employed.



The demand for tertiary N,N-dimethylamines as synthetic intermediates in the Hofmann elimination and the Cope elimination[16] prompted us to examine the general synthetic utility of this reaction for preparing tertiary amines. Our experiments are summarized in Table I. The reaction gave a good yield with a relatively hindered bicyclic ketone and appears to be quite general for cyclic ketones. Its use in the preparation of *endo*-2-dimethylaminonorborane is worthy of note since this compound has previously been prepared only by a multistep route.[17,18] Likewise the reaction afforded reasonable yields of tertiary amines with methyl ketones. However, as the acyclic ketones become more highly substituted, the yields decreased. For example 3-pentanone afforded a 38% yield of N,N-dimethyl-1-ethylpropylamine, and considerably lower yields were obtained with diisopropyl ketone, 4-heptanone, benzophenone, and α-tetralone. However, no effort was made to increase the yields in these cases by altering the reaction conditions or by the use of Lewis acid catalysis.[9,10] This reaction appears to be the method of choice for the conversion of cyclic and relatively unhindered acyclic ketones into tertiary amines because of the ease of manipulation and the good yields of easily purified products.

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Experimental Section

An Example of a Procedure for the Synthesis of Tertiary Amines in Table I. N,N-Dimethylcyclooctylamine.—To a glass-lined[19] high pressure autoclave, arranged for agitation by rocking, was placed 100 g (0.79 mol) of cyclooctanone, 100 g of 90.5% formic acid, and 175 g of dimethylformamide. The autoclave was heated at 190°, under autogenous pressure, for 16 hr. The autoclave was allowed to cool and was vented in a hood.

The pale yellow homogeneous solution was slowly added to a separatory funnel containing 500 ml of a 10% hydrochloric acid solution and the aqueous amine hydrochloride was washed several times with ether.[20] The aqueous phase was treated with a solution of 70 g of sodium hydroxide in 200 ml of water (basic to litmus paper) and the N,N-dimethylcyclooctylamine was recovered by extracting with two 500-ml portions of ethyl ether. The ethereal layer was dried ($MgSO_4$) and the ether was removed under reduced pressure to afford 98 g of crude amine as a light-colored oil.

The amine was distilled under reduced pressure through a short Vigreux column. The product was collected at 63° (3 mm), $n^{25}D$ 1.4710 [lit.[15] bp 79–80 (6 mm), $n^{25}D$ 1.4706].

Cycloheptyltrimethylammonium Iodide.—In a glass-lined high pressure autoclave was placed 56.1 g (0.5 mol) of cycloheptanone, 64 g of 90.5% formic acid, and 110 g of dimethylformamide. The autoclave was heated at 190° for 14 hr and then was cooled to room temperature.

The pale yellow solution was slowly added to a separatory funnel containing 300 ml of 10% hydrochloric acid solution. The aqueous amine hydrochloride was extracted twice with 250-ml portions of ethyl ether. The aqueous layer was cooled and sodium hydroxide was added until the solution was decidedly basic. The N,N-dimethylcycloheptylamine was recovered by extracting with two 250-ml portions of ethyl ether. The ethereal layer was dried ($MgSO_4$) and the solvent was removed, at reduced pressure.

The crude amine was converted into its methiodide without further purification. Methyl iodide (100 g) was added dropwise to a stirred solution of the crude amine in 150 ml of methanol maintained at 0°. The ice bath was removed and the reaction mixture was stirred 3 hr at room temperature. The yellow solution was then poured into 1 l. of ethyl ether, filtered, and washed with ethyl ether to give 101 g (71.3%) of cycloheptyltrimethylammonium iodide that had mp 263.5–264° dec (lit.[21] mp 259°).

Registry No.—I, 15924-18-2; II, 15924-19-3.

(19) When the reaction was carried out in a stainless steel high-pressure autoclave without the use of a glass liner, the yield of product was greatly reduced and a considerable amount of cyclooctanol was obtained as the major product.

(20) The combined ether layers were dried ($MgSO_4$) and the ether was removed under pressure to afford 21 g of an approximately 1:1 mixture of cyclooctanone and cyclooctanol.

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Oxidations of Amines. V. Duality of Mechanism in the Reactions of Aliphatic Amines with Permanganate[1]

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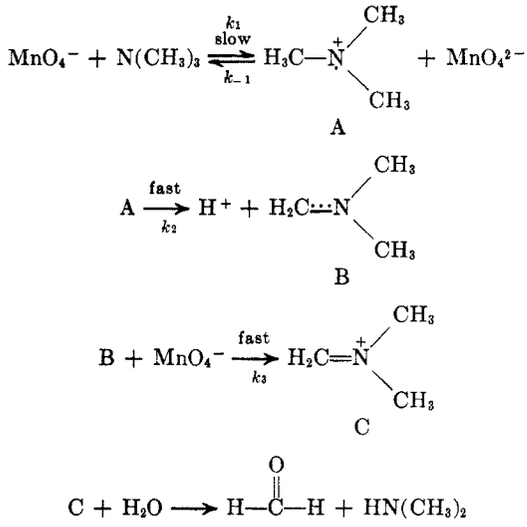
The mechanism of permanganate oxidation of aliphatic amines, *i.e.*, electron *vs.* hydrogen atom or hydride abstraction in the rate-determining step k_1, as well as the relative reactivities of aliphatic primary, secondary, and tertiary amines with permanganate ion in nearly neutral aqueous solutions are unresolved questions of current interest.[2,3] Whereas one would infer from an early investigation by Vorländer, Blau, and Wallis[4] that the order of reactivity should be tertiary > secondary > primary, Lambert and Jones have quoted the opposite conclusions[2a] from the literature.[2b] This confusion may be the result of a reversal in order of reactivity on change from neutral to acidic permanganate. Stewart[5] has stated that oxidation of trimethylamine by permanganate involves an initial attack on the C–H bond adjacent to the nitrogen.

Recognizing the similarity between permanganate and chlorine dioxide[6] oxidation of aliphatic amines, we tentatively propose, for discussion purposes, the mechanism in Scheme I for permanganate oxidation of trimethylamine. The manganate formed in Scheme I reacts to give manganese dioxide as in eq 1. This

SCHEME I



$$3MnO_4^{2-} + 2H_2O \longrightarrow 2MnO_4^- + MnO_2 + 4OH^- \quad (1)$$

reaction is too fast to enter into the kinetics under the pH conditions chosen for this study.[3] The product, formaldehyde, has been detected. This product is analogous to the benzaldehyde obtained by Wei and Stewart[3] from permanganate oxidation of benzylamine; as was shown by these investigators, the reactive amine species is the free base.

Our experience with chlorine dioxide in amine oxidations[6] led us to believe that both α-hydrogen atom transfer and electron transfer mechanisms can occur simultaneously, depending on the structure of the amine, on the oxidizing species, etc. Indeed, benzylamine, studied by Wei and Stewart,[3] is one of the most likely amines to react by α-hydrogen transfer, both because it is a primary amine (see below) and because

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