give dark, polymeric tars and only an 18.4% yield of IIb was obtained. Three additional recrystallizations of the above crude solid from 95% ethanol gave pure product as a greyish-white solid, m.p. 202-202.5°. $\lambda_{\rm max}$ 229 (60,500), 270 (5,380), 281 (7,570), 292.5 (8,560), and 309 m μ (6,700).

Anal. Caled. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.71; N, 5.28. Found: C, 76.72; H, 5.66; N, 5.33.

1-β-Phenethyl-2(1H)-pyridone (IV). A mixture of 1.5 g. (0.81 mmole) of phenethyl bromide and 2.0 g. (1.62 mmoles) of 2-ethoxypyridine was heated at 128–130° with stirring for 48 hr. At the end of this time, 50 ml. of water was added and the mixture was steam distilled. To the cooled residue was added saturated sodium hydroxide solution until a strongly basic solution was obtained. This solution was extracted with three 100-ml. portions of chloroform; the combined chloroform layers were dried over magnesium sulfate and filtered. After removal of the solvent, the residual brownish oil was crystallized from benzene-ligroin to give 1.23 g. (76.5%) of white platelets, m.p. 100–102°. Two further recrystallizations of this solid from benzene-ligroin gave the pure pyridone, m.p. 104.5–105°.¹⁸ λ_{max} 299 (5,675) and 305 mμ (4,460).

1-(\$-6-Methoxy-1-naphthylethyl)-2-chloropyridinium iodide (III). A solution of 350 mg. (1.25 mmoles) of IIa in 5 ml of anhydrous benzene was refluxed with 2 ml. of phosphorus oxychloride for 3 hr. The reaction mixture was cooled and treated with a large excess of petroleum ether. After 1 hr. in the refrigerator, the solvent was decanted from the pale yellow oil which had settled to the bottom. The oil was dissolved in 7 ml. of 0.2N hydrochloric acid and the resulting clear solution was warmed and treated with excess of a saturated aqueous potassium iodide solution. The precipitate was filtered, washed well with cold water, dried, and recrystallized from ethanol to give 363 mg. (68.2%) of fine yellow needles, m.p. $195-197^{\circ}$ (dec.). When the reaction was performed in xylene according to the directions of Wiley, Smith, and Knabeschuh,²¹ a 59.5% yield of III was obtained, m.p. 195-197° (dec.). Three additional recrystallizations of the above material from ethanol gave pure quaternary iodide, m.p. 200-201° (dec.). λ_{max} 228 (60,700), 268 (7,700), 275 (8.820), 317 (2,100), and 331.5 m μ (2,230).

Reaction of III with aqueous sodium hydroxide. To a mixture of 147 mg. (0.346 mmole) of III in 10 ml. of water was added a solution of 250 mg. (6.25 mmoles) of sodium hydroxide in 3 ml. of water. The solution was heated on the steam bath for 2 hr. After cooling the mixture, it was extracted with three 10-ml. portions of chloroform. The organic layers were combined, washed with water, and dried over magnesium sulfate; filtration and evaporation of this solution yielded a dark brown oil which was crystallized from ligroin-benzene (decolorized with Norit) to give 85 mg. (88.5%) of a white solid, m.p. 100-102°. Three additional recrystallizations of this material from benzene-ligroin gave white crystals, m.p. 104-105.5°. A mixed melting point determination of this material with a sample of the pure pyridone IIa showed no depression; the elemental analysis was also in agreement with this structure.

Reaction of 1-(β -6-methoxy-1-naphthylethyl)-2(1H)-pyridone (IIa) with anhydrous hydrogen bromide. Into a solution of 558 mg. (2.0 mmoles) of IIa in 5 ml. of glacial acetic acid was passed a steady stream of anhydrous hydrogen bromide. The solution was slowly heated to reflux and was refluxed for 0.5 hr. The acetic acid was removed under reduced pressure and the residual brown oil was crystallized from ethanol-ether to give 475 mg. (77.7%) of white crystals, m.p. 185-187° (gas evolution). Three further recrystallizations of this solid from ethanol-ether gave an analytical sample of the hemihydrobromide of IIb, m.p. 187-187.5° (gas evolution).

Anal. Calcd. for C₁₇H₁₆NO₂·¹/₂ HBr: C, 66.77; H, 5.11; N, 4.58. Found: C, 66.69; H, 5.31; N, 4.63.

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A small sample of the above material was warmed on the steam bath for 15 min. with concentrated ammonium hydroxide. After extracting the reaction mixture with chloroform, the combined organic layers were dried over magnesium sulfate, filtered, and evaporated to yield a residue which was crystallized from ethanol to give pale yellow crystals, m.p. $197-199^{\circ}$. This material, on admixture with an authentic sample of IIb, m.p. 202° , gave a melting point of $197-199^{\circ}$; the infrared spectra of the two samples were identical.

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Structures Related to Morphine. XXI.¹ An Alternative Synthesis of Diastereoisomeric 2'-Hydroxy-2,5,9-trimethyl-6,7-

benzomorphans

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Cyclization of 2-(*p*-methoxybenzyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine with 48% hydrobromic acid leads to a mixture of diastereoisomeric benzomorphans IV and VI in a ratio of about 12:1, respectively.³ The analgesic activity (in mice) of the lesser isomer (VI) was seven times that of IV and five times that of morphine.³ Furthermore, VI had little if any abstinence-suppressing capacity in the monkey in an established morphine addiction.⁴ Consequently, a more extensive study of this compound and relatives seemed warranted, and a more satisfactory method of preparation was therefore sought.

Efforts to increase the yield of VI in the abovementioned ring closure have, to date, been unsuccessful. Thus we centered our attention on the 9methylcarbinol (I),⁵ the demethoxy relative of which had previously been converted (in low yield) to 2,5,9-trimethyl-6,7-benzomorphan⁶ by catalytic hydrogenation of the corresponding 9-methylene derivative. By a similar sequence of reactions we can now obtain either IV or VI³ depending upon the medium used in the hydrogenation of the 9methylene compound (II).

(1) Paper XX, S. Saito and E. L. May, J. Org. Chem., 27, 948 (1962).

(2) Visiting scientist from Osaka, Japan.

(3) E. L. May and J. H. Ager, J. Org. Chem., 24, 1432 (1959). For convenience compounds III and IV (methyl oriented away from nitrogen) will be designated α and V, and VI designated β . NMR and methiodide-rate-formation studies (to be published) confirm our original, tentative configurational assignments.

(4) Personal communication from Dr. G. Deneau, Department of Pharmacology, University of Michigan.

(5) E. L. May and H. Kugita, J. Org. Chem., 26, 188 (1961).

(6) E. L. May and E. M. Fry, J. Org. Chem., 22, 1366 (1957).



Reaction of I with thionyl chloride in great excess (pyridine as catalyst) afforded II in 75% yield. Hydrogenation (platinum oxide) of II or the hydrochloride salt in ethanol proceeded relatively rapidly producing, in 73% yield, the methyl ether III, as shown by its conversion to IV, the predominant isomer obtained in the Grewe synthesis from 3,4-lutidine.^{3,6} If, however, the hydrogenation were conducted in alcohol containing 15% hydrochloric acid, the direction of hydrogen addition was reversed and a 70% yield of the racemate V was obtained. O-Demethylation of V gave the desired VI in 70% yield. Finally, hydrogenation of the methiodide (VII) of II, with absorption of nearly two molar equivalents of hydrogen, resulted principally in opening of the nitrogen ring (Emde degradation). The open nitrogen compound (IX) proved to be isomeric, but not identical, with either cis-6 or trans³-1,2-dimethyl-7-methoxy-1-(2 - dimethylaminoethyl) - 1,2,3,4 - tetrahydronaphthalene. Also isolated in low yield from this experiment was a methiodide (VIII) isomeric but not identical with either III or V methiodide. Their structures remain unknown; apparently there has been skeletal rearrangement.

EXPERIMENTAL

Melting points were taken in a capillary Hershberg-type apparatus. Microanalyses are from the institutes' service analytical unit. Harold McCann, Director. Infrared spectra are by H. K. Miller and Ann Wright, also of this institute.

2'-Methoxy-2,5-dimethyl-9-methylene-6,7-benzomorphan (II) hydrochloride. Thionyl chloride (50 ml.), 1 ml. of pyridine, and 5 g. of I⁵ were kept at 40° (bath temperature) with stirring for 50 hr. Evaporation to dryness at the water pump (room temperature) and addition of ice afforded a yellow solution which was made alkaline with concd. ammonium hydroxide and extracted with ether. The dried extract was evaporated and the residue evaporatively distilled at a bath temperature of 180-200°/1 mm., giving 4.5 g. of crude II. This yielded 4.0 g. (75%) of hydrochloride salt; needles (from ethanol-ether) m.p. 253-256°, $\lambda_{\rm misi}^{\rm Nuisi}$ 6.05 and 10.7 μ .

Anal. Calcd. for $C_{16}H_{22}^2$ ClNO: C, (8.68; H, 7.93; Cl, 12.67.Found: C, (8.62; H, 8.06; Cl, 12.95.

The methiodide of II (VII) crystallized from methanol in flakes, m.p. 234-236° (dec.); $\lambda_{\text{max}}^{\text{Nuloi}}$ 10.7 μ .

Anal. Calcd. for $C_{17}H_{24}$ INO: C, 52.99; H, 6.28; N, 3.64. Found: C, 53.13; H, 6.35; H, 3.50.

 α -2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan (III) hydrochloride.³ Ethanol (10 ml.), 0.3 g. of II hydrochloride,⁷ and 0.15 g. of platinum oxide absorbed 1 equiv., of hydrogen during 1 hr. The filtered solution was evaporated to dryness at the water pump and the residue digested with acetone giving 0.25 g. (73%) of III hydrochloride, m.p. 160-162°. The infrared spectrum (λ_{musl}^{nusl} 2.95, 3.13 μ) and analytical data indicated it to be a hemihydrate.

Anal. Calcd. for $C_{16}H_{24}CINO + \frac{1}{2} H_2O$: C, 66.08; H, 8.66; N, 4.82. Found: C, 66.27; H, 8.63; N, 4.63.

 α -2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (IV). The hydrochloride of III (0.2 g.) and 2.3 ml. of 48% hydrobromic acid were refluxed for 15 min., cooled, made alkaline with aqueous ammonia, and extracted with chloroform. Evaporation of the chloroform *in vacuo* left a residue which crystallized from methanol in a yield of 0.11 g. (70%), m.p. 233-238°. This base and its hydrochloride were indistinguishable (m.p., crystal form, infrared spectra) from authentic IV and its hydrochloride.⁶

 β -2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan (V) hydrochloride. (a) From authentic VI. Authentic VI was methylated with diazomethane as described before.³ The hydrochloride salt of V crystallized from ethanol-ether in rods, m.p. 230– 233°.

Anal. Calcd. for C₁₆H₂₄ClNO: C, 68.20; H, 8.58. Found: C, 68.02; H, 8.84.

(b) From II. Platinum oxide (0.06 g.), 0.35 g. of II hydrochloride, 20 ml. of 15% hydrochloric acid,⁸ and 10 ml. of ethanol absorbed 1 equiv. of hydrogen during 1.5 hr. The filtered solution was evaporated to dryness *in vacuo*. The sirupy residue crystallized from acetone in a yield of 0.25 g. (70%). It was indistinguishable (m.p. phenomena, infrared, etc.) from the authentic V hydrochloride prepared as described above.

 β -2'-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (VI). The IV hydrochloride prepared from II was O-demethylated as described for III above to give 71% of VI, m.p. 215-217.5° identical (m.p., IR, etc.) with authentic VI.⁸ Furthermore, the hydrochloride (difficultly soluble in methanol, a property diagnostic for the base VI) was indistinguishable from authentic hydrochloride.³

Hydrogenation of VII. Platinum oxide (0.3 g.), 1.2 g. of VII, and 40 ml. of methanol absorbed 1.7-1.8 equiv. of hydrogen during 18 hr. The filtered solution was evaporated to dryness at the water pump. The residue, treated with acetone, gave 0.1 g. of methiodide (VIII) cubes from

⁽⁷⁾ Hydrogenation of II (base) gave almost identical results.

⁽⁸⁾ Perchloric acid (15%) could be used in place of hydrochloric acid.

methanol-water, m.p. $273-275^{\circ}$ (dec.).⁹ The filtrate was evaporated to dryness. The residue was partitioned between dilute aqueous ammonia and ether. Evaporation of the dried ether solution and distillation of the residue at 0.2 mm. gave 0.55 g. (72%) of a colorless oil (IX) whose hydrobromide salt crystallized from acetone in needles, m.p. 184-187°.

Anal. Calcd. for $C_{17}H_{28}BrNO$: C, 59.64; H, 8.24; N, 4.09. Found: C, 59.67; H, 8.06; N, 4.19.

The picrate of IX, prisms from methanol-acetone, melted at 152-153°.

Anal. Caled. for $C_{23}H_{30}N_4O_8$: C, 56.32; H, 6.17; N, 11.42. Found: C, 56.32; H, 6.24; N, 11.54.

 β -7-Methoxy-1,2-dimethyl-1-(2-dimethylaminoethyl)-1,2,-3,4-tetrahydronaphthalene picrate. As described before³ authentic V methiodide was degraded to this compound whose picrate melted at 149-150° and was markedly depressed in m.p. by IX picrate.

Anal. Calcd. for $C_{23}H_{30}N_4O_8$: C, 56.32; H, 6.17. Found: C, 56.25; H, 6.45.

The hydrobromide salt (m.p. 194-196°) of this authentic tetrahydronaphthalene derivative was also depressed in melting point by the hydrobromide of IX. Furthermore, the picrate and hydrobromide of IX proved to be different from these salts prepared by Hofmann degradation of authentic III and reduction of the resultant methine.³

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(9) Although the found carbon-hydrogen values (C, 53.01; H, 6.56) for the methiodide VIII were in agreement with those calculated for VII, the infrared spectrum and melting point were clearly different from the starting VII. In addition, VIII was different from the methiodide of either III or V (cf. ref. 3).

Formation of Isocyanides during the Thermal Decomposition of Sodium Trichloroacetate in the Presence of Arylamines

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Two general synthetic methods to isocyanides have been utilized most extensively since their discovery by Hofmann¹ and Gautier.² These methods consist of the action of silver cyanide on alkyl iodides and the reaction of chloroform-base on primary amines.³ More recently Ugi⁴ has published some excellent isocyanide syntheses by dehydration of monosubstituted formamides with phosphorus oxychloride. The chloroform-base reaction on primary amines is well known and is used qualitatively to distinguish between primary and secondary amines by making use of the disagreeable odor of isocyanides which are formed on reaction of primary amines.⁵ The intermediacy of dichlorocarbene in the formation of isocyanides from primary amines is substantiated by the investigations of Hine.⁶ The reaction of dichlorocarbene (from potassium t-butoxide and chloroform) with secondary and tertiary amines has been reported by Saunders⁷ and Frankel.⁸ The decarboxylation studies of Hine⁹ on chlorodifluoroacetic acid in aqueous solution led to a proposed concerted decomposition to diffuoromethylene. Most other trihaloacetate ions lose carbon dioxide to yield the trihalomethyl anion which is subsequently protonated by the medium. It has been demonstrated by Wagner¹⁰ that the thermal decomposition of sodium trichloroacetate in nonprotonic solvents leads to dichlorocarbene as an intermediate (trapped in the presence of olefins). This method of formation of dichlorocarbene was investigated in the presence of aryl amines as trapping agents. In a preliminary test a distinct odor of phenyl isocyanide could readily be detected by refluxing aniline and sodium trichloroacetate in 1,2-dimethoxyethane for a few minutes. The odor of the isocyanide could also be detected on heating aniline and sodium trichloroacetate without solvent for a few minutes. A more detailed study of this decomposition showed that fair yields of isocyanides could be obtained. The results of this investigation are listed in Table I.

TABLE I

	Molarity ^a			
Amine	Amine	Sodium trichloroacetate	Hours Refluxed	$_{ m RNC}^{\%}$
Aniline p-Toluidine p-Toluidine p-Anisidine	1.1 1.6 1.0 1.0	$ \begin{array}{r} 1.1 \\ 3.2 \\ 3.0 \\ 3.0 \\ 3.0 \\ \end{array} $	$ \begin{array}{r} 16 \\ 6 \\ 3/4 \\ 1/2 \end{array} $	15 ^b 25 ^b 43 ^c 38 ^c

^a All runs are in dry 1,2-dimethoxyethane as solvent. ^b The infrared spectrum showed the presence of unchanged amine and the % isocyanide is estimated from the strong isocyanide band at 4.70 μ . ^c The infrared spectrum shows the material to be pure isocyanide.

The optimum yield of the isocyanide can be obtained utilizing a 3:1 molar ratio of sodium trichloroacetate to amine and is not contaminated by unreacted amine. Unchanged amine was found to be present in runs having less than a 3:1 molar ratio of sodium trichloroacetate to amine. Undoubtedly this arises from the reaction of CCl_3 -

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