recovery) of white solid, mp 79–85°. Recrystallization from ethanol–water gave material with mp 84–86°, mmp 84–86° with methyl *p*-tolyl sulfone. The infrared spectrum was also identical with that of methyl *p*-tolyl sulfone.

Reactions of *p*-Tolylsulfonyl Isocyanate (VII). A. With Phenylmagnesium Bromide. Forward Addition.—Phenylmagnesium bromide was prepared from 4.08 g (0.026 mole) of bromobenzene and 0.59 g (0.024 g-atom) of magnesium in 20 ml of dry ether. The solution of Grignard reagent was cooled in ice and to it was added with stirring and under nitrogen a solution of 4.33 g (0.022 mole) of VII in 30 ml of dry ether during 20 min. The mixture of white precipitate and pink solution was stirred at ice temperature for an additional 30 min and then for 4 hr at room temperature.

The mixture was hydrolyzed with 100 ml of 0.5 *N* hydrochloric acid solution. A white precipitate appeared and was filtered off: 1.57 g (26.0%), mp 145–147°. Work-up of the filtrate and final removal of solvent from the organic layer gave 4.23 g of greasy solid. Swirling with benzene and filtering afforded 3.03 g (50.0%) of white solid, mp 144–147°. Since infrared and mixture melting point showed the two samples to be identical, they were combined (total yield 76.0%) and recrystallized from benzene to constant mp 147–148°, lit.[17] mp 147° for N-(*p*-tolylsulfonyl)-benzamide (VIII). Infrared absorption peaks at 3400 and 1715 cm^{-1} indicated N–H and carbonyl. Nmr peaks at τ 7.72 (3 H) and 0.92 (1 H) were evidence for the tolyl methyl group and N–H, respectively, in addition to phenyl hydrogen peaks.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.09; H, 4.73. Found: C, 61.20; H, 4.69.

A similar reaction was run except that a 1:2 ratio of isocyanate to Grignard reagent was used. The yield of VIII was 70.5%.

A forward additon reaction with a 1:1 isocyanate to Grignard reagent ratio was carried out in which the ether was allowed to reflux during addition and the mixture was heated under reflux for an additional 2.5 hr. The yield of VIII was only 34.1%. The other product was a red oil.

Inverse Addition.—Phenylmagnesium bromide prepared from 4.08 g (0.026 mole) of bromobenzene and 0.59 g (0.024 g-atom) of magnesium in 20 ml of dry ether was added to a solution of 4.33 g (0.022 mole) of VII in 30 ml of dry ether during 20 min at ice temperature. After stirring at 0° for 30 min and at room temperature for 4 hr, the mixture was hydrolyzed with 100 ml of 0.5 *N* hydrochloric acid solution. The oily solid which precipitated was collected and amounted to 6.19 g. Swirling with 50 ml of 1:2 benzene–petroleum ether gave 4.54 g (75.1%) of crystals, mp 140–144°. Recrystallization from benzene gave VIII with constant mp 147–148°, identical by infrared and mixture melting point with the VIII above. Removal of the solvent from the original organic layer gave an intractable yellow oil, with infrared bands at 3600, 3300, 1740, and 1690 cm^{-1}.

An identical reaction was run except that the ether was allowed to reflux during addition and the mixture was subsequently heated under reflux for 2.5 hr. The yield of VIII was 70.8%.

B. With Methylmagnesium Iodide. Forward Addition.—A solution of 4.33 g (0.022 mole) of VII in 30 ml of dry ether was added with stirring under nitrogen during 20 min at 0° to the methylmagnesium iodide prepared from 3.69 g (0.026 mole) of iodomethane and 0.59 g (0.024 g-atom) of magnesium in 20 ml of dry ether. The mixture was stirred at 0° for 30 min and at room temperature for 4 hr. Upon hydrolysis with 50 ml of 1 *N* hydrochloric acid solution a white precipitate formed and was collected: 1.90 g (41.0%), mp 138–139.5°. Recrystallization from benzene–petroleum ether gave N-(*p*-tolylsulfonyl)acetamide (IX) with constant mp 138.5–139°, lit.[18] mp 139°. Strong infrared absorption was observed at 3250 and 1720 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.70; H, 5.16. Found: C, 50.59; H, 5.10.

Removal of solvent from the original ether layer gave 2.20 g (47.4%) of solid, mp 120–130°. Recrystallization from benzene–petroleum ether gave material with constant mp 138.5–139°, and identical by infrared and mixture melting point with the IX above.

Acknowledgment.—The authors wish to thank the Department of Chemistry and Chemical Engineering of the University of Illinois for the nmr spectra.

(17) A. D. Kemp and H. Stephen, *J. Chem. Soc.*, 110 (1948).

(18) G. Kresze and B. Wustrow, *Ber.*, **95**, 2652 (1962).

New Benzomorphan Ring Closure in the Synthesis of 5-Phenylbenzomorphans

GORDON N. WALKER AND DAVID ALKALAY

Research Department, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey

Received January 17, 1966

Base-catalyzed, internal N-alkylation of amides of 2-bromo-4-(carboxymethyl)-4-phenyl-1-tetralone is stereospecific and gives 5-phenylbenzomorphan-3,8-diones. These keto lactams have been converted, by reduction *via* 8-hydrazone or by stepwise hydrogenolysis involving 8-chloro intermediates, to 5-phenylbenzomorphan-3-ones, and then by hydride reductions into the corresponding benzomorphans.

Synthesis of quaternary carbon compounds structurally related to morphine is a field of durable interest to many chemists. Of a number of approaches which have been followed, four (Scheme I, A–D) have been particularly successful in duplicating all or part of the morphine structure. (A) The Grewe piperideine → morphinan cyclization[1] has been extended to synthesis of a number of morphinans, isomorphinans and benzomorphans.[2] (B) Reductive closure of 1,2-tetralindione-4-acetonitriles to isomorphinans,[3] key to the first total synthesis of morphine, has been used in synthesis of other isomorphinans.[2,3] (C) Displacement of a suitable leaving group (OAc) β to nitrogen on a chain appended to a 2-aminotetralin system, by a carbanion which becomes the quaternary carbon atom, led to morphinans and a second total synthesis of morphine.[4] (D) Displacement of 2-bromo in a 1- or 3-tetralone system by quaternization of a β-dialkylaminoethyl chain appended at quaternary carbon 4 has also been employed as a route to benzomorphans.[2,5] With this work there are to be grouped other less practical, if scarcely less interesting, attempts to synthesize quaternary carbon analogs and precursors of the morphine

(1) R. Grewe, *Angew. Chem.*, **59**, 194 (1947); R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948).

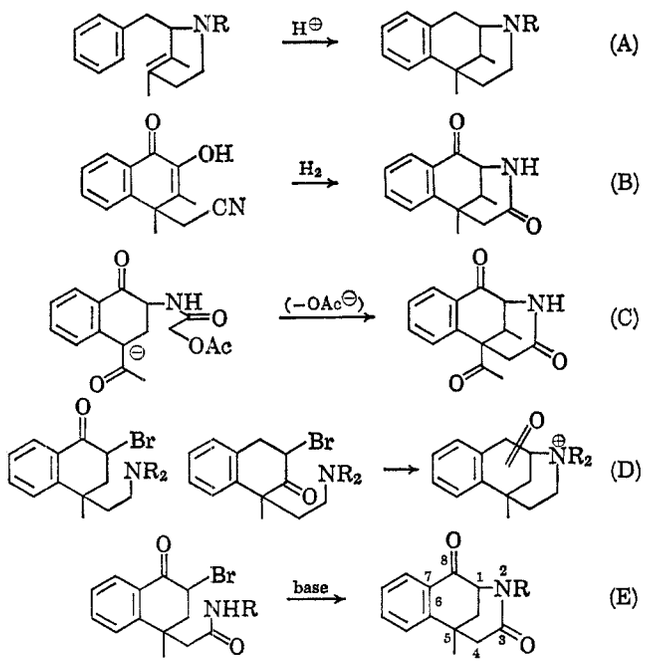
(2) E. L. May and L. J. Sargent ("Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 4) present a detailed review of this subject.

(3) M. Gates, R. B. Woodward, W. F. Newhall, and R. Künzli, *J. Am. Chem. Soc.*, **72**, 1141 (1950); M. Gates and W. F. Newhall, *ibid.*, **70**, 2261 (1948); M. Gates, *ibid.*, **72**, 228 (1950); M. Gates and G. Tschudi, *ibid.*, **72**, 4839 (1950); **74**, 1109 (1952); **78**, 1380 (1956); M. Gates and W. G. Webb, *ibid.*, **80**, 1186 (1958).

(4) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 938 (1951); 1524 (1953); D. Elad and D. Ginsburg, *J. Am. Chem. Soc.*, **76**, 312 (1954); *J. Chem. Soc.*, 3052 (1954).

(5) J. A. Barltrop, *ibid.*, 399 (1947); J. A. Barltrop and J. E. Saxton, *ibid.*, 1038 (1952); E. L. May and J. G. Murphy, *J. Org. Chem.*, **20**, 257 (1955); J. G. Murphy, J. H. Ager, and E. L. May, *ibid.*, **25**, 1386 (1960).

SCHEME I
REPRESENTATION OF
MORPHINAN AND BENZOMORPHAN SYNTHESIS



skeleton,[6] as well as similar syntheses of phenylmorphans,[2] isomeric morphinans with nitrogen at bridgehead and other positions,[2] and chromans having a nitrogen-containing bridge similar to that of benzomorphans.[7]

In all the remarkably long record of work on synthetic analgetics,[8] until very recently no one seems to have dwelt on the possibility of synthesizing a 5-aryl-substituted benzomorphan,[9] and on reflection one might construe this as a notable omission. It is obvious that such a compound would include skeletal features of both benzomorphan and of normethadone, superimposed upon the "analgetiphoric" moiety. The purpose of this paper is to describe the finding of yet another method (E) for benzomorphan ring closure and its specific application to 5-phenylbenzomorphans.

There was at hand a precursor **1b**, containing the necessary carbon atoms, prepared[10,11] by the well-precedented[12] alkylation of benzene with γ-carboethoxy-γ-phenylbutyrolactone followed by cyclization, as shown in Scheme II.[13] The introduction of nitrogen conceivably could be accomplished by β nitrosation of the tetralone. However, our early efforts to nitrosate **1b** gave not only 2-isonitroso derivative **2a**, but also 2-nitro compound **2b**, evidently formed through oxidation by excess reagent during the slow reaction,[14] and attempts to reduce compounds **2** led to very unpromising yields of bridged lactam. It would have been even more laborious to convert **1** through a series of reactions to a corresponding 4-(cyanomethyl)tetralin-1,2-dione, to which presumably the Woodward–Gates reductive closure (B) might be applied. A better and more novel plan was adopted, following the work of Schenker, in which there was projected closure of the bridged ring through displacement of 2-bromo group by an amide.[15]

When attention was directed to preparing amides from compounds **1** it was first found that these could not be obtained readily *via* reaction of the acid **1a** with thionyl chloride and then with amines, possibly because of interfering spirocyclization of the acid chloride.[16] However, aminolysis of ester **1b** with ammonia or methylamine proceeded smoothly, albeit slowly, giving **3a** and **b**, respectively. Bromination of the amides was then carried out, in benzene and tetrahydrofuran as preferred solvents. The brominated product from **3a** was a mixture of the two diastereoisomers, **4a** and **5a**, both of which eventually were obtained in crystalline form. Similar results were obtained in bromination of the N-methylamide **3b**, although in this case only one isomer, later assigned structure **5b**, could be isolated in crystalline form. Also, in the latter case, a by-product, evidently acyloin **7** judging from analytical results and spectra, was formed, presumably through intervening solvolysis of the bromo compound during work-up. No by-product of this kind was found accompanying **4a** and **5a**.

Cyclization of the bromoamides with sodium methoxide[15] was tried initially with the mixture of isomers **4a** and **5a**, and gave keto lactam **6a** in rather low yield. Compound **6a** was isolated readily, however, owing to its comparatively low solubility in methanol. Later, after **4a** and **5a** had been isolated individually, improved experiments showed that only the higher melting isomer **5a** led to **6a** with sodium methoxide. Considering that intramolecular reaction of –Br with –CON< very likely involves backside (SN2 type) attack, one is led to assign the *trans* Br–amide structure **5a** to the higher melting, cyclizing isomer.[17] The crystalline fraction obtained from bromination of **3b** evidently is **5b**, corresponding stereochemically to **5a**, since it too was ring closed with sodium methoxide to give **6b**. The residual bromo-N-methylamide, presumably **4b**, did not give **6b**. Rather there was iso-

(6) L. F. Fieser and H. L. Holmes, *J. Am. Chem. Soc.*, **58**, 2319 (1936); **60**, 2548 (1938); M. S. Newman and M. D. Farbman, *ibid.*, **66**, 1550 (1944); M. S. Newman and R. D. Closson, *ibid.*, **66**, 1553 (1944); M. S. Newman and B. Magerlein, *ibid.*, **69**, 942 (1947); C. F. Koelsch, *ibid.*, **67**, 569 (1945); E. C. Horning and R. U. Schock, *ibid.*, **70**, 2941, 2945 (1948); G. Stork and H. Conroy, *ibid.*, **73**, 4743, 4748 (1951); G. B. Bachmann and L. B. Wick, *ibid.*, **72**, 3388 (1950); G. B. Bachmann and E. J. Fornefeld, *ibid.*, **73**, 51 (1951); B. Belleau, *ibid.*, **75**, 1159 (1953); D. Elad and D. Ginsburg, *J. Chem. Soc.*, 2664 (1953).

(7) H. E. Zaugg, R. W. De Net, and E. T. Kimura, *J. Med. Pharm. Chem.*, **5**, 430 (1962); U. S. Patent 3,118,900 (1964).

(8) In addition to references already cited, see earlier reviews by F. Bergel and A. L. Morrison, *Quart. Rev.* (London), **2**, 349 (1948); E. S. Stern, *ibid.*, **5**, 405 (1951); R. A. Hardy and M. G. Howell, ref 2, Chapter 5.

(9) See J. R. Geigy, Belgian Patents 657,405 and 657,406 (1965); *Chem. Abstr.*, **64**, 2067 (1966).

(10) W. Herz and G. Caple, *J. Org. Chem.*, **29**, 1691 (1964).

(11) G. N. Walker, D. Alkalay, and R. T. Smith, *ibid.*, **30**, 2973 (1965).

(12) W. Herz and G. Caple, *J. Am. Chem. Soc.*, **84**, 3517 (1962), and references therein.

(13) A possible alternative to standard Reformatsky synthesis of butyrolactones of this required type is reaction of β-acyl- or β-aroylbutyric esters with $(C_6H_5)_3P{=}CHCOOEt$ or a similar ylid.

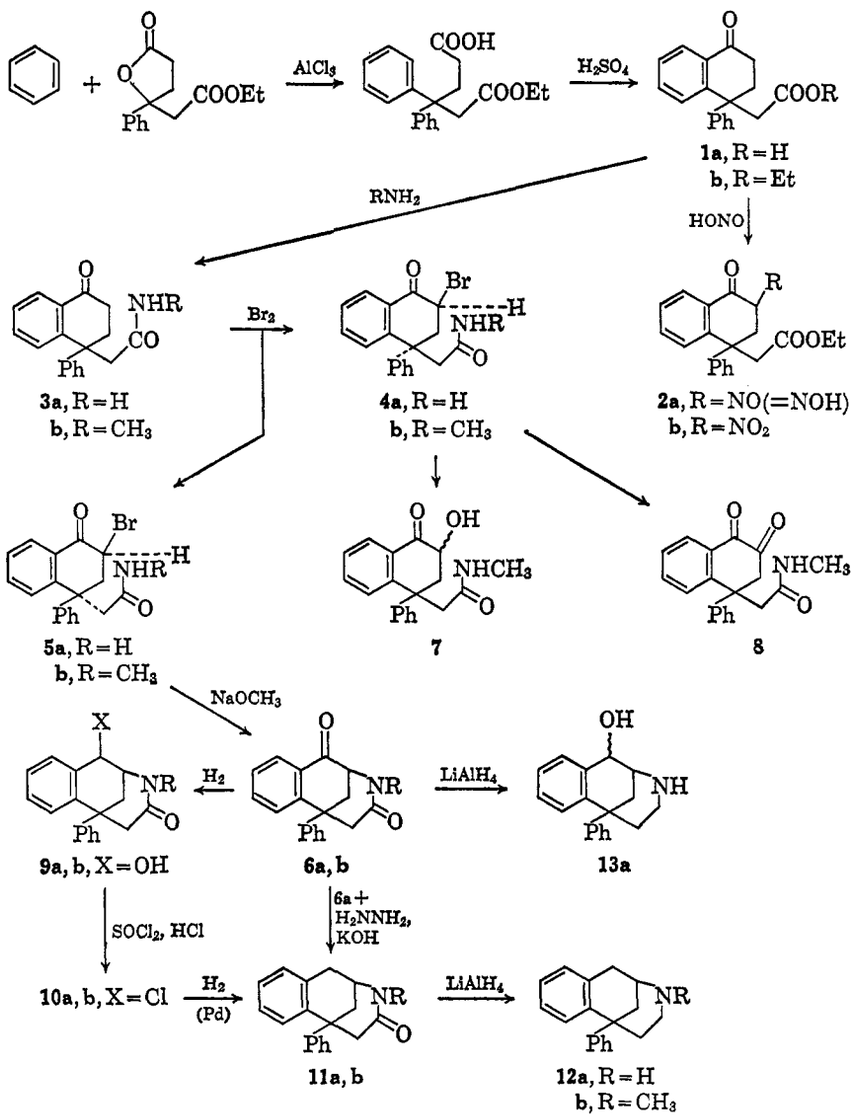
(14) H. Feuer and R. S. Anderson, *J. Am. Chem. Soc.*, **83**, 2960 (1961).

(15) K. Schenker, *Tetrahedron Letters*, in press; see also Belgian Patent 665,189 (1965). In private communications we were apprised of the cyclization of 2-bromo-4-carboxamido-1-tetralones to 1-substituted 2,3,4,5-tetrahydro-1,4-methano-1H-3-benzazepine-2,5-diones.

(16) Herz and Caple[12] successfully prepared amides from the acid chloride corresponding to 4-methyl-4-(carboxymethyl)-1-tetralone. The 4-phenyl compound, however, is inclined to spirocyclize readily.[10,11]

(17) Neither infrared nor ultraviolet spectra of **4a** and **5a** add any further evidence for the assigned stereo structures, since they are, respectively, very similar. Significant pmr spectra could not be obtained because of the lack of a suitable inert solvent. However, general considerations, models, and presumed analogy with other cases[15] have made it appear likely that both **4a** and **5a** exist primarily as conformers in which the 2-bromo group is equatorial and the 4-phenyl group is, respectively, axial and equatorial.

SCHEME II



lated, after its treatment with methoxide, a compound which from spectra and analysis evidently was diketone **8**, formed *via* solvolysis and air oxidation in the basic medium.

Infrared spectra of bicyclic keto lactams **6a** and **b** clearly showed that an NH band had disappeared in going to them from the precursor amides in each case, and other features of infrared spectra (separate and intense tetralone 5.9–5.95-μ and six-membered lactam *ca.* 6.05-μ bands) and ultraviolet spectra (in each case, characteristic tetralone maxima at *ca.* 250 and 294 mμ with respective ϵ values of *ca.* 10,000 and 2350) were consonant with the structures **6**.[18]

With a view to correlating the two series, **a** and **b**, of lactams and providing the necessary additional evidence for structure, reduction of compounds **6** was then explored. Direct lithium aluminum hydride reduction of **6a** was found to give only a poor yield of carbinolamine **13a**, together with a certain amount of hydroxy lactam **9a**, and similar treatment of **6b** did not give a hydroxy bicyclic amine, but rather led to what may have been a bridged carbinolamine (see Experimental Section). These reductions, each involving both ketone and lactam groups, are incomplete even in refluxing tetrahydrofuran, and the evidence indicates that they tend to proceed as far as an 8-hydroxy bicyclic carbinolamine or enamine which is trapped, possibly because of formation of insoluble, corresponding lithium aluminum salts, or may undergo further, abnormal changes in the course of isolation.

Both better results and clear evidence for structure were obtained when hydrogenolysis of compounds **6** was undertaken. In the presence of palladium on charcoal (at 80°) and acetic acid, compounds **6a** and **b** were not hydrogenolyzed completely but afforded the 8-hydroxy lactams, **9a** and **b**, respectively. This behavior contrasts markedly with the facile hydrogenolysis under these conditions observed[11] in 1-tetralones having no 2 substituents and is analogous to similar reductions leading to 1-aryl-1-hydroxy-2-alkylamines.[19]

Hydroxy lactams **9** were treated next with thionyl chloride in order to obtain the more readily hydrogenolyzed, corresponding 8-chloro lactams, **10**. The comparative resistance of the hydroxy group in com-

(18) Because of their interposed methylene group, compounds **6** do not show that splitting of ultraviolet benzoyl band into 230- and 260-mμ components owing to parallel interaction of carbonyl groups which is observed[15] in the sterically more rigid, analogous, bridged five-membered lactams.

(19) W. H. Hartung and J. C. Munch, *J. Am. Chem. Soc.*, **51**, 2262 (1929); G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 432 (1961); G. N. Walker, *ibid.*, **27**, 2966 (1962); F. Zymalkowski, *Pharm. Ztg., Ver. Apotheker-Ztg.*, **107**, 1228 (1962).

pounds **9** to displacement was again evident in these reactions: as in similar, bridged hydroxy five-membered lactams,[15] corresponding 8-chloro sulfites which were formed initially appeared to be unusually stable. Avoiding, at this point, bases which might have disturbed the lactam ring, we found that the intermediate chlorosulfites were converted smoothly by alcoholic hydrogen chloride to the 8-chloro lactams, **10**. The latter were then hydrogenolyzed in the presence of palladium on charcoal, giving the 8-desoxy lactams, **11**. Methylation of **11a** in the presence of sodium hydride then readily gave **11b**, identical with that from **10b** hydrogenolysis, establishing the structural correlation of the two series, and finally lithium aluminum hydride reduction of lactams **11** provided the amines **12**. An alternative and shorter route to the amines, as well as further evidence confirming structures **6**, was found in Huang-Minlon-modified Wolff–Kishner reduction[3,4] of keto lactam **6a**, which provided lactam **11a** directly (54% yield). Lithium aluminum hydride reduction of **11a** was complicated by the difficulty that a short reaction time gave a low yield of **12a**, evidently because of formation of an excessively insoluble metal salt, while prolonged reduction led to other reactions, probably involving rearrangement or degradation, as detailed in the Experimental Section. However, after N-methylation, the hydride reduction of **11b** seemed relatively free of complications.

It also deserves to be mentioned that the N-methyl-8-chloro lactam **10b** was never successfully purified, and, although suitable as an intermediate for preparation of **11b**, it proved to be less stable than the corresponding N-demethylchloro compound **10a**. It tended to undergo further changes, of a nature also presently obscure but possibly involving ring opening, and rearrangement or cyclization in another direction. It was also observed that prolonged hydrogenation of crude **10b** resulted in the formation of a lactam, $C_{19}H_{25}NO$, in which phenyl apparently was reduced to cyclohexyl. For these reasons, as well as those already mentioned, routes involving **11a** and its N-alkylation are the preferred ones.

There seems to be little doubt that the routes found here in proceeding from a 4-carboxamidomethyl-1-tetralone to a benzomorphan might be useful in other related cases.

Compound **12b** was disappointing as an analgetic, being only moderately active at 25 mg/kg in the tail-flick test and toxic or lethal at doses of 50–75 mg/kg in rodents.

Experimental Section[20]

Amides Derived from 4-Carboxymethyl-4-phenyl-1-tetralone.—Preparation of the ethyl ester corresponding to this keto acid on a moderately large scale was described earlier.[11] A solution of 41.0 g of the ethyl ester in 1400 ml of ethanol and 2000 ml of concentrated NH_4OH was allowed to stand at room temperature for 6 days, then was evaporated on steam bath to a volume of *ca.* 1000 ml. The amide **3a** was collected, washed with water, and air dried: yield 34.6 g (93%) of crystals; mp 150–151° initially (solvated), not raised on drying or recrystallization from ether but lowered to 146–147°; λ_{max}^{Nujol} 2.92, 3.12, 5.88, and 5.98 μ; λ_{max}^{EtOH} 249 and 295 mμ (ϵ 11,380 and 2070, respectively).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.50; H, 6.11; N, 5.01.

The corresponding N-methylamide **3b** was prepared similarly from 46.0 g of 4-carboethoxymethyl-4-phenyl-1-tetralone using 750 ml of ethanol and 1500 ml of 40% aqueous methylamine. After standing 1 week, the solution was evaporated to a volume of *ca.* 1200 ml and treated with 300 ml of water. The crude product which separated was taken up in enough ether to render the crystals free of oily material, and the crystals were collected in three crops, totaling 32 g (73%), mp 150–152°. After recrystallization from ether there was obtained a sample of colorless crystals: mp 154–156°; λ_{max}^{Nujol} broad and intense 2.94 μ and broad doublet 5.9–5.96 and 6.10 μ; λ_{max}^{EtOH} 249 and 293 mμ (ϵ 11,050 and 1880, respectively).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.84; H, 6.53; N, 4.78.

2-Isonitroso-4-carboethoxymethyl-4-phenyl-1-tetralone (2a).—A solution of 5.1 g of keto ester **1b** in 100 ml of dry ether was saturated with anhydrous hydrogen chloride at 0° and then treated slowly with 3 ml of butyl nitrite. After standing at 0–20° for 5 hr, the solution was washed several times with water, dried ($MgSO_4$), and evaporated. The residue partly crystallized after several days, and with the aid of a little ether there was obtained *ca.* 0.8 g of light yellow crystals, mp 169–175°. A sample after recrystallization from ethanol had mp 182.5–183.5°, gave a weak red ferric chloride test, and was soluble in dilute sodium hydroxide solution: λ_{max}^{Nujol} broad, strong hydroxyl band and peaks 5.78 and 5.96 μ; λ_{max}^{EtOH} 273 mμ (ϵ 13,740).

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.23; H, 5.60; N, 4.09.

The remaining, crude, orange, viscous material obtained in this experiment was base soluble and ferric chloride positive, but gave no additional crystalline material on standing in the presence of various solvents. Hydrogenation of the crude material (4 g) in glacial acetic acid (100 ml) in the presence of 10% palladium on charcoal at 3 atm and 75° for 4 hr resulted in uptake of 2–3 molar equiv of hydrogen; after filtration and evaporation there was obtained oily material which darkened in the presence of air. From this crude material, after it had stood several days in the presence of acid, there was obtained a small amount (*ca.* 0.1 g) of crystalline product which, after recrystallization from methanol–ether, had mp 290–293° dec; λ_{max}^{Nujol} very broad hydroxyl band centered at *ca.* 2.65 μ, and intense peak at 6.14 μ; λ_{max}^{EtOH} 258–265 and 272 mμ (ϵ 450 and 310, respectively) with inflections at 252 and 268 mμ. These results and analysis indicated that the material was an isomer of **8-hydroxy-5-phenylbenzomorphan-3-one**.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.04; H, 6.19; N, 4.90.

The yield of this lactam was not improved in repetitions of the experiment, and the route was not investigated further.

2-Nitro-4-carboethoxymethyl-4-phenyl-1-tetralone (2b).—Reaction of 5 g of **1b** with 3 ml of isoamyl nitrite in 100 ml of ether saturated with dry HCl was carried out as described in the preceding experiment, except that after the initial period of reaction at ice temperature, the solution was allowed to stand at room temperature overnight. The crystals (3.8 g) which separated, together with remaining crude material, were taken into ether–ethyl acetate, and the solution was washed with sodium bicarbonate solution and water, dried, and evaporated. The crude product, 2.9 g (50%), had mp 131–135°, raised on recrystallization from ether to 134–136°; λ_{max}^{Nujol} 2.85 (w), 2.94 (w), 5.77, 6.05, and 6.39 μ; λ_{max}^{EtOH} 238, 306, and 351 mμ (ϵ 13,760, 3900 and 4140, respectively), with inflection at 264 mμ.

Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.92; H, 5.18; N, 3.92, 4.16.

Catalytic reductions of this compound under various conditions did not provide crystalline products.

2-Bromo-4-carboxamidomethyl-4-phenyl-1-tetralone.—Bromination of amide **3a** was carried out a number of times, best results being obtained as follows. To a solution of 23.2 g of **3a** in 2000 ml of reagent benzene and 400 ml of tetrahydrofuran was added, during 0.5–1.0 hr, a solution of 13.5 g of bromine in 75 ml of tetrahydrofuran. There was an initial induction period (5–10 min) and during this time the solution was warmed gently on a steam cone to help initiate the reaction, after which the bromine was taken up readily. The solution was diluted with ether, washed with three portions of sodium bicarbonate

(20) Melting points, requiring no appreciable correction, were obtained using a rapidly stirred, coil-heated, Thomas–Hoover-type silicone oil bath. Infrared spectra were measured in the Perkin-Elmer double-beam instrument, and ultraviolet curves were obtained using Beckman recording spectrophotometer. Unless otherwise noted, samples for analysis were dried at 80° *in vacuo* (*ca.* 0.05 mm).

solution and three portions of water, dried ($MgSO_4$), and evaporated to a small volume. Crystals began to separate when the volume of the solution was reduced to *ca.* 700 ml; they were collected in a series of crops, and the remaining solution was evaporated to smaller volume after each filtration. The combined, first four crops of bromoamide, after methanol–ether trituration, had a melting point ranging from 160 to 170° and a total weight of 12.3 g (41%) and consisted almost exclusively of the higher melting isomer, **5a**. A pure sample was prepared by recrystallization from methanol: colorless crystals; mp 169–170°; λ_{max}^{Nujol} 2.92, 3.14, 5.94, and a subsidiary peak 6.12 μ; λ_{max}^{EtOH} 252 and 294 mμ (ϵ 11,400 and 2060, respectively).

Anal. Calcd for $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91. Found: C, 60.39; H, 4.36; N, 3.74.

Evaporation of the solution remaining after separation of the first crystalline fractions gave discolored, oily material; that this consisted of a mixture of **5a** and lower melting isomer **4a** was shown in one instance by isolation of a further small amount of **5a** through trituration with ether–methanol, and in another instance by cyclization of the total fraction with sodium methoxide to furnish a *ca.* 9% yield of 5-phenylbenzomorphan-1,3-dione, as described below.

Before compound **5a** was obtained in crystalline form as described above, the lower melting isomer **4a** was isolated first in an earlier, similar experiment. After bromination of 5.6 g of amide **3a** with 3.2 g of bromine in a total of 550 ml of benzene and 250 ml of tetrahydrofuran and work-up as described above, solvents were evaporated and the residue was taken up in ether; the solution was filtered clear of a small amount of solids which separated initially and was allowed to evaporate again. The now partly crystalline residue was triturated with methanol, and there was collected 1.5–2 g of crystals, mp *ca.* 140–150°. Recrystallization from methanol gave a pure sample: mp 150–151.5°; mmp, with **5a**, 138–145° (depressed); λ_{max}^{Nujol} 2.91, 3.17, 5.93, and a shoulder at 6.06 μ, not identical with spectrum of **5a**; λ_{max}^{EtOH} 253 and 293 mμ (ϵ 10,740 and 2140, respectively).

Anal. Calcd for $C_{18}H_{16}BrNO_2$: C, 60.34; H, 4.50; N, 3.91. Found: C, 60.13; H, 4.44; N, 3.86.

Compounds **4a** and **5a**, as well as **5b** prepared as described in the following experiment, gave strong qualitative tests for bromine.

N-Methyl-2-bromo-4-carboxamidomethyl-4-phenyl-1-tetralone (5b).—A solution of 32 g (0.109 mole) of N-methylamide **3b** in 3000 ml of benzene was prepared by warming the suspension on a steam cone. The addition of a solution of 18 g (0.112 mole) of bromine in 100 ml of benzene was begun while the solution of amide was still warm, and thereafter continued during 15–20 min without further heating. After 20 min, the cooled solution was washed with three portions of sodium bicarbonate solution and several portions of water, dried ($MgSO_4$), and evaporated. The first crop of crystals (7.4 g) from the concentrated benzene solution had mp 148–156°, and a second crop (6.5 g), mp 146–154°, was obtained from the residue, after evaporation, using methanol–ether. The total yield was 13.9 g (34%). A pure sample, obtained by recrystallization from methanol, had mp 160–162°; λ_{max}^{Nujol} 3.05 (s), 3.23 (w), 5.89, and 6.12 μ, with a shoulder at 6.00 μ; λ_{max}^{EtOH} 253 and 291 mμ (ϵ 10,510 and 2110, respectively).

Anal. Calcd for $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87; N, 3.76. Found: C, 61.15; H, 4.93; N, 3.64.

A lower melting, crystalline isomer, **4b**, of this bromoamide was not found in the residues remaining after separation of the above crystals. Instead, successive additional crops of crystalline material, obtained from the mother liquors through use of methanol–ether and totaling *ca.* 3.5 g, had melting points of 210° and higher; recrystallization of this material from methanol gave what appeared to be **N-methyl-2-hydroxy-4-carboxamidomethyl-4-phenyl-1-tetralone (7)**, as pale yellow crystals: mp 214–215°; λ_{max}^{Nujol} 2.87 (s, shouldered), 5.90, and 6.06 μ (intense); λ_{max}^{EtOH} 250, 294, and 324–338 mμ (ϵ 10,250, 2500, and 320, respectively).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 74.50; H, 5.79; N, 4.41.

5-Phenyl-6,7-benzomorphan-3,8-dione (6a).—Initially, this compound was isolated in low yield (24–36%) after cyclization of a sample of total, crude bromination product from **3a** consisting of an impure mixture of **4a** and **5a**. Later, after isomer **5a** had been isolated, an improved procedure was developed, as follows. Bromoamide **5a**, 12.3 g of the mp 160–170° fraction obtained as described above, was refluxed 3 hr with a solution of 5 g of sodium in 100 ml of methanol. The methanol was removed by distillation on a steam cone *in vacuo*, and the cooled residue was treated with water. The crystals which separated were collected, washed with water and with methanol, and air dried: yield 6.0 g (63%), mp 256–259° dec. Recrystallization from methanol gave slightly yellow crystals: mp 257–259° dec; λ_{max}^{Nujol} 3.02 (br, moderate, with shoulders at *ca.* 3.12 and 3.25 μ), an intense, unresolved doublet 5.92 and 6.02 μ, and sharp, moderate peak 6.26 μ; λ_{max}^{EtOH} 247–250 and 294 mμ (ϵ 10,510 and 2350, respectively). The sample gave a negative Beilstein test for bromine.

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.81; H, 5.53; N, 4.98.

Another experiment, carried out in the same way, in which 5.3 g of purer **5a**, mp 167–169°, was cyclized using a solution of 2.0 g of sodium in 30 ml of methanol, gave 3.6 g (93%) of the same **6a**, mp 256–259° dec.

Attempts to N methylate this lactam, using methyl iodide and sodium hydride or sodium methoxide, were unsuccessful.

An attempt to compress the operations **3a** → **4a** + **5a** → **6a** by first brominating **3a** in methanol and then treating with sodium methoxide gave poor results. From 5.6 g of **3a** there was isolated only 0.5 g of impure **6a** and, in addition, 5 g of crystalline material, mp *ca.* 124–130°, analysis, spectra, and qualitative tests of which indicated that it consisted of a mixture of bromo and methoxy compounds: λ_{max}^{Nujol} broad 2.94–3.12 and intense 6.01–6.12 μ.

Anal. Found: C, 59.25; H, 5.57; Br, 20.34; N, 3.34.

2-Methyl-5-phenylbenzomorphan-3,8-dione (6b).—Similar cyclization of 13.9 g of bromoamide **5b**, the crystalline portion from bromination of **3b**, with a solution of 5.7 g of sodium in 600 ml of methanol by refluxing 3 hr, followed by removal of methanol *in vacuo* and treatment with water and ammonium chloride solution, gave crystalline material which was collected, washed with water, and dried. The yield of slightly yellow, crude keto lactam, mp 186–190°, was 9.3 g (86%). Recrystallization from methanol gave a colorless sample, mp 187–190°, having negative test for halogen: λ_{max}^{Nujol} intense 5.88 and 6.06 μ, moderate 6.22 μ; λ_{max}^{EtOH} 250, 294, and 338–344 mμ (ϵ 10,020, 2380, and 260, respectively).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.40; H, 5.80; N, 4.73.

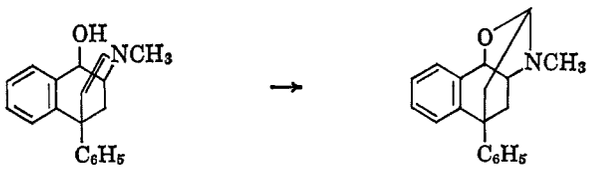
A portion of the oily fraction remaining after preparation of bromoamide **5b** (1.5 g) was also treated with sodium methoxide (from 0.8 g of sodium) in methanol (150 ml) and refluxed for 1 hr. In addition to a small amount of **6b** there was isolated 0.5 g of a less methanol-soluble, yellow, crystalline substance, mp 253–256°, evidently **N-methyl-4-carboxamidomethyltetralin-1,2-dione (8)**. Purified by recrystallization from methanol, this sample had mp 262–264°; λ_{max}^{Nujol} 2.97, 5.77, 5.93, and 6.13 μ; λ_{max}^{EtOH} 236–242, 302, and 360 mμ (ϵ 10,490, 3520, and 4590, respectively).

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.06; H, 5.02; N, 4.51.

Reduction of a sample (2.9 g) of keto lactam **6b** with lithium aluminum hydride (8 g) in tetrahydrofuran (750 ml) was carried out by refluxing and stirring for 6 hr. After treatment with water (60–70 ml), filtration, and evaporation of the solvent, a solution of the organic residue in ether was extracted with 18% HCl to remove basic product. Addition of dilute KOH solution to the acid extract, ether extraction, drying (K_2CO_3), and evaporation gave a crude amine from which, using ether, there was obtained 0.8 g of somewhat unstable, crystalline base, mp *ca.* 130–135°. Recrystallization from ether afforded a pure sample, as colorless crystals, mp 145–148°. Since the material turned pink on heating, it was dried *in vacuo* at room temperature. The infrared spectrum (Nujol) was devoid of any appreciable OH, NH, or carbonyl bands, but indicated slight polar character and had a weak band at *ca.* 6.23 μ as well as the usual (705 cm^{-1}) monosubstituted phenyl peak. The ultraviolet spectrum with λ_{max}^{EtOH} 258, 264, and 273 mμ (ϵ 710, 700, and 480, respectively), also lacked any indication of conjugated unsaturated groups other than phenyl.

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.48, 82.41, 82.45; H, 6.96, 6.66, 6.90; N, 5.07, 4.93.

Since this compound evidently was neither an aminocarbinol nor a completely saturated, cyclic amine, it may have had the following structure, formed by interaction of carbinol and eneamine groups.



Unstable, noncrystalline materials resulted from treatment of this compound with acetic anhydride or hydrogen chloride.

8-Hydroxy-5-phenylbenzomorphan-3-one (**9a**).—Hydrogenation of a solution of 3 g of 5-phenylbenzomorphan-3,8-dione in 250 ml of glacial acetic acid in the presence of 3 g of 10% palladium on charcoal at 60–70° and 3 atm for 7 hr, followed by repetition of the procedure using 3 g of fresh catalyst for 7 hr longer, filtration, and evaporation of the solvent, gave crude, crystalline material which, on trituration with ether and recrystallization from methanol–ether, afforded 1.3 g of colorless crystals, mp 210–214°. Recrystallization from methanol gave a pure sample: mp 216–217°; λ_{max}^{Nujol} broad 3.08 and intense 6.09 μ; λ_{max}^{EtOH} 258 and 268 mμ (ϵ 420 and 320, respectively) with low inflections at 251, 264, and 272 mμ.

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.14; H, 5.84; N, 4.97.

In scaling up this experiment, 7.3 g of keto lactam was hydrogenated in 300 ml of acetic acid in the presence of 7 g of 10% palladium on charcoal, at 80° and 50 psi pressure for 5 hr. The pressure drop having indicated the uptake of 2.2 molar equiv of hydrogen, the product was isolated by filtration and evaporation. The product in this case (7.2 g) had mp *ca.* 140–147° after trituration with ether and may have been solvated, polymorphic, or a mixture of isomers; however, it was suitable for use in further reactions, as described next.

8-Chloro-5-phenylbenzomorphan-3-one (**10a**).—The product (7.2 g) from the preceding experiment was refluxed 0.5 hr with 80 ml of thionyl chloride. The excess reagent was removed at 100° *in vacuo*. The residual yellow crystals, probably a chlorosulfite, had mp *ca.* 183–188°, gave a strong elemental test for sulfur, and could not be purified successfully. They were treated with 100 ml of 5% ethanolic hydrogen chloride, and this solution was warmed on a steam cone for about 15 min until evolution of sulfur dioxide ceased. Evaporation afforded the crude 8-chloro compound, suitable for use directly in hydrogenolysis. A sample of the material was purified by first dissolving it in warm, dry ether, filtering the solution, and evaporating the solution to a smaller volume. The yellowish crystals which separated were collected and recrystallized from benzene–ethyl acetate: colorless crystals; mp 268.5–270.5° dec; λ_{max}^{Nujol} shoulders at 3.15 and 3.3 μ, intense peak at 5.98 μ; λ_{max}^{EtOH} 260, 265, 270, and 277 mμ (ϵ 560, 620, 680, and 540, respectively). The compound gave a very strong Beilstein test for chlorine.

Anal. Calcd for $C_{18}H_{16}ClNO$: C, 72.60; H, 5.42; N, 4.70. Found: C, 72.62; H, 5.69; N, 4.70.

5-Phenylbenzomorphan-3-one (**11a**).—Identical samples of this compound were obtained by two methods.

A.—A solution of 6 g of crude chloro compound from the preceding experiment in 300 ml of ethyl acetate and a few milliliters of 5% ethanolic HCl was boiled to remove remaining traces of sulfur dioxide. After cooling, 6 g of 10% palladium on charcoal was added, and the suspension shaken under hydrogen (50 psi) at 75° for 3.5 hr; a pressure drop (in a 4-l. system) of 2 lb was observed. Filtration, evaporation of the colorless solution, and trituration of the crystalline residue with ethyl acetate gave 4.5 g (79% from hydroxy lactam) of crystals: mp 243–246°, raised by recrystallization from the same solvent to 247–249°; λ_{max}^{Nujol} 3.15, 3.82, and 6.03 μ; λ_{max}^{EtOH} 252, 258, 265, 269, and 273 mμ (ϵ 370, 460, 440, 470, and 250, respectively); negative test for chlorine.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.27; H, 6.63; N, 5.27.

B.—A solution of 7.4 g of 5-phenylbenzomorphan-3,8-dione and 33.5 g of KOH (85%) in 300 ml of diethylene glycol was treated with 63 ml of 95% hydrazine and distilled slowly until reflux temperature rose to 188°, then refluxed 2 hr. The cooled solution was poured over ice, and the separated solid was collected, washed with water, air dried, and recrystallized from ethyl acetate. There was obtained 3.8 g (54%) of lactam, mp 239–245°, raised on further recrystallization to 246–249°. The mixture melting point with a sample from A was undepressed, and the infrared and ultraviolet spectra were identical.

2-Methyl-5-phenyl-8-hydroxybenzomorphan-3-one (**9b**).—Hydrogenation (45 psi) of 5.0 g of **6b** in 250 ml of glacial acetic acid in the presence of 3 g of 10% palladium on charcoal at 80° for 6 hr, followed by filtration and evaporation, gave crude material which crystallized in the presence of methanol and afforded 3.3 g of material, mp 215–234°. A pure sample, obtained by recrystallization from methanol, had mp 230.5–233°; λ_{max}^{Nujol} broad and intense 2.99 and intense 6.23 μ; λ_{max}^{EtOH} 261 and 269 mμ (ϵ 380 and 270, respectively) with low inflections at 252 and 270 mμ.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.00; H, 6.60; N, 4.74.

2-Methyl-5-phenylbenzomorphan-3-one (**11b**).—The N-methyl lactam also was obtained in two ways, either by hydrogenolysis of the corresponding 8-chloro compound or by methylation of the corresponding secondary lactam as follows.

A.—A 0.5-hr reflux of 3.8 g of hydroxy-N-methyl lactam from the preceding experiment with 90 ml of thionyl chloride, followed by distillation of the excess reagent on a steam cone *in vacuo*, gave a brown, viscous, sulfurous residue. This material was treated with 100 ml of 5% ethanolic HCl and the solution was warmed on a steam cone for 10 min; when the evolution of SO_2 was complete, the solution was evaporated. Several attempts to isolate a pure sample of this intermediate chloro compound, using ether and other media, gave only a small amount of an ill-characterized and somewhat unstable, crystalline solid, melting point varying from *ca.* 158 to 213° dec, which could not be purified successfully. It was also observed that prolonged action of thionyl chloride, or excessive heating during work-up, led rather easily to some further change of the chloro compound, partly into a crystalline substance of unknown character: mp (after recrystallization from benzene) 163–165°; infrared (Nujol), 6.06 μ, not converted to desired product in the next step.

Anal. Found: C, 72.33; H, 7.64; N, 4.51; Cl, 12.85.

Therefore a solution of the crude chloro compound in 300 ml of ethyl acetate was hydrogenated immediately in the presence of 3.5 g of 10% palladium on charcoal at 45 psi and 75° for 4 hr; since the crude product from this manipulation did not crystallize, the procedure was repeated using 3 g of fresh catalyst. Filtration and evaporation then gave a readily crystallizing residue, trituration of which with ether afforded 1.4 g of colorless crystals, mp 167–172°. Recrystallization from ethyl acetate gave a pure sample: mp 175–176°; λ_{max}^{Nujol} 6.08–6.10 μ; λ_{max}^{EtOH} 260–265 and 272 mμ (ϵ 430–460 and 240, respectively) with a shoulder 269 mμ (ϵ 310).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05. Found: C, 82.59; H 7.05; N, 5.17.

An experiment, in which reaction of **9b** (6.3 g) with thionyl chloride (150 ml) was prolonged to 2.5 hr and the crude product not treated with alcoholic HCl, gave 3.3 g of the aforementioned crystals, mp 163–165° after recrystallization from benzene–ligroin (bp 40°). This material also was subjected to hydrogenation in ethyl acetate in the presence of 10% palladium on charcoal at 75–80° for 12 hr, with one change of catalyst after 6 hr. Thin layer chromatographic analysis (silica gel G) of the resulting crude product indicated a mixture consisting of five components. The main product, isolated using ether–ethyl acetate and recrystallized from methanol–ether, had mp 102–104°, λ_{max}^{Nujol} 6.10 μ; and no NH or OH bands.

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.51; H, 8.47; N, 5.07.

Lithium aluminum hydride reduction of the crude mixture from which this lactam was obtained gave two isolable products. The first, a neutral compound but evidently not a lactam, consisted of colorless crystals: mp (after recrystallization from methanol–ether) 240–241°; λ_{max}^{Nujol} 2.86–2.94 (doublet), 3.92 (br), and 6.16 μ; λ_{max}^{EtOH} 265 mμ (ϵ 290).

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.44; H, 8.92; N, 4.51.

The second product, a base, formed a picrate, yellow crystals from ethanol, mp 168.5–170.5°, not pure but probably for the most part the same as the picrate of 2-methyl-5-phenylbenzomorphan described below.

Anal. Found: C, 60.80; H, 5.95; N, 11.38.

B.—A suspension of 5 g of 5-phenylbenzomorphan-3-one and 3 g of 56% sodium hydride–Nujol dispersion in 750 ml of toluene was stirred and refluxed for 1 hr, cooled, treated with 23 ml of methyl iodide, then stirred and refluxed 6.5 hr. After cautious treatment of the cooled suspension with water, the organic layer was diluted with ether, washed several times with water,

dried ($MgSO_4$), filtered, and evaporated. The residue, recrystallized from methanol–ether, gave 4.7 g of crystals, mp 173–175°, mmp, with product from A, 173–174° (undepressed); the infrared spectra were identical.

Wolff–Kishner reduction of 2-methyl-5-phenylbenzomorphan-3,8-dione did not give this compound but resulted in extensive decomposition.

2-Methyl-5-phenylbenzomorphan (12b).—Reduction of 4.5 g of lactam from the preceding experiments with 15 g of lithium aluminum hydride in 500 ml of tetrahydrofuran, carried out by refluxing and stirring 7 hr and worked up by slow addition of 75 ml of water to the chilled suspension, filtration, and evaporation of the solvent, gave a crude amine fraction, which crystallized in the presence of ether and afforded 2.7 g of colorless crystals, mp 96–97°. This melting point was not raised by recrystallization from ether: λ_{max}^{EtOH} 259 mμ (ε 530); devoid of infrared OH, NH, or carbonyl absorption.

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.91; H, 8.26; N, 5.27.

The **picrate**, yellow crystals from ethanol, had mp 178.5–179.5°.

Anal. Calcd for $C_{25}H_{24}N_4O_7$: C, 60.97; H, 4.91; N, 11.38. Found: C, 60.93; H, 4.89, N, 11.32.

The **methiodide**, prepared by refluxing 0.6 g of amine with 10 ml of methyl iodide in 120 ml of methanol for 5 hr and recrystallized from methanol, had mp 274–276° dec and appeared to be slightly hygroscopic. The sample was dried at 100° *in vacuo*.

Anal. Calcd for $C_{20}H_{24}IN$: C, 59.26; H, 5.97; I, 31.35; N, 3.46. Found: C, 58.27; H, 5.93; I, 31.15; N, 3.48.

Another experiment, in which the lactam was reduced with lithium aluminum hydride on a smaller scale, gave a crude, partly crystalline basic fraction from which there was obtained the same picrate, mp 178–179°, identical by mixture melting point and infrared spectrum, as obtained in the experiment above. In this case the base itself, after crystallization from ether, had mp *ca.* 150–175° dec and appeared from analysis to be a hydrate or carbonate.

Anal. Found: C, 80.92; H, 7.41; N, 4.99, 4.50.

The melting point of this base is reported recently[9b] to be 158–159°. The apparent discrepancy in results may be due to polymorphism, differences in degree of solvation, or the existence of two isomers of the N-methyl compound.

5-Phenylbenzomorphan (12a).—A mixture of 3.8 g of 5-phenylbenzomorphan-3-one, 12 g of lithium aluminum hydride, and 1000 ml of tetrahydrofuran was refluxed and stirred 8 hr. Dropwise addition of 100 ml of water to the cooled, stirred mixture, followed by filtration, gave a solution, which was evaporated to a small volume (*ca.* 20 ml). With the aid of ether, there was obtained 2.2 g of neutral crystals, mp 257–264°, raised on recrystallization from ethyl acetate to 290–294°, which evidently were a metal salt of the starting lactam. On treatment with dilute hydrochloric acid or methanolic sodium methoxide this material gave 5-phenylbenzomorphan-3-one, mp 246–249°, identical with the authentic sample.

The ether–tetrahydrofuran filtrate, after removal of the above salt, was evaporated. A filtered, ether solution of the crude residue was extracted with 100 ml of 10% hydrochloric acid. The acid extract was made basic by addition of 10% sodium hydroxide solution, and the crude base was extracted with ether. The ether solution was dried (K_2CO_3), filtered, and evaporated. The crude base (*ca.* 1.0 g), an opalescent oil, did not crystallize, but tended to absorb carbon dioxide and/or moisture from the air.

The corresponding **N-acetyl derivative**, prepared by warming a sample of the crude base 15 min with acetic anhydride and recrystallized from ether, had mp 134–136°.

Anal. Calcd for $C_{23}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.41; H, 7.30.

The **hydrochloride**, poorly crystalline and evidently hygroscopic, was recrystallized from acetone; after drying *in vacuo* at 80° the hemihydrate was obtained: mp 278–279° (lit.[9b] mp 277–278°); λ_{max}^{Nujol} weak, broad bands at 3.00 and, *inter alia*, 4.00 μ; λ_{max}^{EtOH} 257, 264, and 273 mμ (ε 435, 420, and 230, respectively).

Anal. Calcd for $C_{18}H_{20}ClN \cdot 0.5H_2O$: C, 73.33; H, 7.18; N, 4.75. Found: C, 73.50; H, 7.17, 6.92; N, 4.88.

Further drying at 100° *in vacuo* resulted in nearly complete disappearance of infrared band at *ca.* 3.00 μ and gave a hygroscopic sample, mp 283–285° dec, with the following analysis.

Anal. Calcd for $C_{18}H_{20}ClN$: C, 75.64; H, 7.05. Found: C, 74.88; H, 7.05.

Attempts to improve the yield of the amine by prolonging (40 hr) the time of lithium aluminum hydride reaction *gave instead a different, neutral product of unknown structure*, mp 310–312°, evidently a **hydroxy lactam**: λ_{max}^{Nujol} 3.04, 3.15, 3.29, and 5.99 μ; ultraviolet (EtOH) benzene bands.[21]

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.52; H, 6.20; N, 5.11.[21]

In addition, there was obtained in this experiment a crystalline **hydroxyamine**,[21] which may or may not correspond in structure to the foregoing lactam: colorless crystals, mp 198–199°, λ_{max}^{Nujol} 3.05 and 3.26–3.30 μ.

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.52, 81.37; H, 7.20, 7.18; N, 5.39.

The **hydrochloride** obtained from this base had mp 200–203° dec after recrystallization from ethanol–ether.

Anal. Calcd for $C_{18}H_{20}ClNO \cdot 0.5H_2O$: C, 69.55; H, 6.81; N, 4.51. Found: C, 69.57; H, 7.02; N, 4.52.[21]

8-Hydroxy-5-phenylbenzomorphan (13a).—Reduction of 3 g of keto lactam **6a** with 5.5 g of lithium aluminum hydride in 250 ml of tetrahydrofuran, by refluxing and stirring for 11 hr, followed by treatment of the cooled suspension with 50 ml of water, filtration, and evaporation of the solvent, gave crude, partly crystalline organic residue which was partitioned between chloroform and dilute hydrochloric acid.

From the chloroform solution, after washing with water, drying ($MgSO_4$), evaporating, and allowing the residue to crystallize in methanol, there was isolated *ca.* 0.3 g of **8-hydroxy-5-phenylbenzomorphan-3-one (9a)**: mp 216–217°; mixture melting point with that obtained through hydrogenolysis of the dione undepressed; infrared spectra identical.

From the acid extract on treatment with dilute KOH solution, a colorless, crystalline base separated; this was collected, washed with water, and air dried. There was obtained 1.0 g of hydrated carbinolamine **13a**, mp *ca.* 100–110°. After recrystallization from ether there were obtained colorless crystals: mp 220–222°; λ_{max}^{Nujol} broad bonded 3.12–3.25 μ, weak polar bands, intact 703-cm^{-1} peak, and no carbonyl peaks; λ_{max}^{EtOH} 258, 264, and 273 mμ (ε 510, 490, and 270, respectively), with inflections at 252 and 268 mμ.

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.87, 80.59; H, 7.25, 7.27; N, 5.23.

Acknowledgment.—We are indebted to Mr. Louis Dorfman and the following members of his staff for microanalytical and spectral data: Mr. George Robertson, Mr. Rudolf Oeckinghaus, Mr. James Mitchell, Mrs. Carol Rodely, Miss Natalie Cahoon, Mrs. Margaret Mulligan, Miss Diane Bonney, and Mr. Charles Navarro. We cordially thank Dr. Karl Schenker, CIBA AG., Basel, for proposing publication of this material in advance of his own work, Drs. E. Schlittler and G. deStevens for their support of the project, and Drs. L. B. Witkin and H. Chernov for pharmacological data.

(21) The analytical results indicate that these abnormal products are still bicyclic compounds, rather than simply 1,2- or 1,8-bond fission and reduction products. A referee suggests that positions 3 and 8 in an intermediate metalloenolate might become involved in bisallylic rearrangement, leading to generation of a carbinolamine function at position 1 and further fission to observed products. As an alternative to such an intermediate, corresponding to the β-tetralone or to the Bredt-rule-intolerable $\Delta^{1,2}$-imine or $\Delta^{1,8}$-enamine, it is also possible that direct, initial interaction of lactam carbonyl with the position 8 (benzylic) anion may lead in the direction of a 1,4-bridged product (aminobicyclooctanone, reduced to corresponding aminocarbinol). In the absence of further information at present, we are reluctant to postulate definitely any of the several possible structures for the hydroxyamide or carbinolamine. However, further study of these contingencies suggests itself.