An Improved Synthesis of a 9-Oxo-6,7-benzomorphan and Its Homolog. A Novel Rearrangement of Heterocyclic Enamines *via* Bromination[1]

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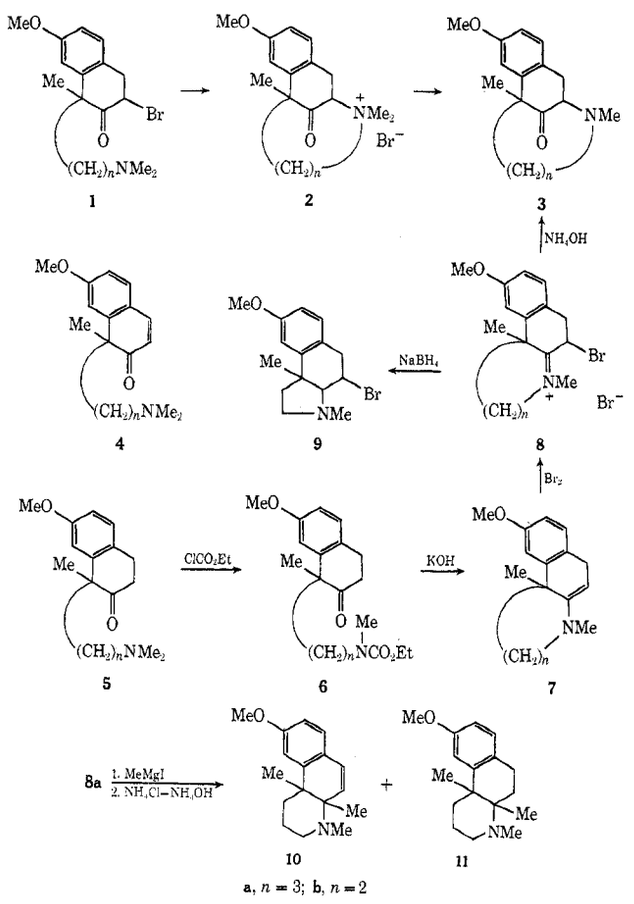
A new synthesis of 2′-methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (**3b**) and its homolog (**3a**) is described. The key step involves bromination of 4,10b-dimethyl-9-methoxy-1,2,3,4,6,10b-hexahydrobenzo[*f*]quinoline (**7a**) and 3,9b-dimethyl-8-methoxy-5,9b-dihydrobenz[*e*]indoline (**7b**). Upon alkalinization with aqueous ammonium hydroxide, the bromination products (**8a,b**) easily underwent rearrangement to **3a,b**, respectively. A possible mechanism of this sequence of reactions is presented.

In our previous paper,[2] 2′-methoxy-2,6-dimethyl-10-oxo-7,8-homobenzomorphan[3] (**3a**), a key intermediate for the synthesis of homobenzomorphan analgesics, was prepared by cyclization of the bromo ketone **1a** followed by pyrolysis. Since the elimination product **4a** was concurrently formed in both steps, **3a** was obtained in rather low yield. A similar observation has been reported in the benzomorphan series[4] (**1b** → **3b**).

We now wish to report a more practical synthesis of **3a** as well as the benzomorphan analog **3b** by a novel rearrangement of the heterocyclic enamines **7a,b** *via* bromination (Scheme I).

SCHEME I



Treatment of 1-(3-dimethylaminopropyl)-7-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone (**5a**)[2] with ethyl chloroformate in benzene[5] yielded the *N*-carbethoxy derivative **6a** in 90% yield, which in turn was heated with potassium hydroxide in 1-butanol to afford the hexahydrobenzo[*f*]quinoline derivative **7a** in 58% yield. The presence of an unsaturated amine absorption at 1655 cm^{-1} and vinyl proton resonance at δ 4.75 (t, 1 H, J = 4 Hz) confirmed the heterocyclic enamine structure of **7a**.

When the enamine **7a** was brominated in methylene chloride[6] and the reaction mixture was treated with aqueous ammonium hydroxide at room temperature, the 10-oxohomobenzomorphan **3a** was obtained in 81% yield.

This new method appeared to be useful also for the synthesis of the benzomorphan analog **3b**. Thus, the dihydrobenz[*e*]indoline derivative **7b** was similarly prepared from **5b** in 48% overall yield. Conversion of **7b** into the 9-oxobenzomorphan **3b** proceeded in 60% yield, without isolation of the intermediate bromo iminium bromide. In another run, this intermediate was isolated in 83% yield; spectral data and elemental analysis (given in the Experimental Section) were compatible with the structure **8b**.

Treatment of **8b** with aqueous ammonium hydroxide gave **3b** in 65% yield. Substitution of anhydrous triethylamine for aqueous ammonium hydroxide in the reaction, however, did not give **3b**. This indicates that hydroxide is essential for the rearrangement.

Sodium borohydride reduction of **8b** gave the saturated bromo amine derivative **9**. Treatment of **9** with aqueous ammonium hydroxide resulted in a quantitative recovery of the material. Upon treating the bromination product **8a** with ethereal methylmagnesium iodide, followed by quenching the Grignard mixture with aqueous ammonium chloride–ammonium hydroxide, the elimination product **10** and the reduction product[7] **11** were obtained. Structural assignments for **10** and **11** were made from their nmr spectra.

Thus, no skeletal rearrangement could be observed by saturation of the iminium double bond in **8**.

Although extensive use of enamine halogenations has been reported in the synthesis of α-halo ketones,[8]

(1) Presented at the 3rd International Congress of Heterocyclic Chemistry, Aug 1971, Sendai, Japan.

(2) M. Takeda and H. Kugita, *J. Med. Chem.*, **13**, 630 (1970).

(3) *Chemical Abstracts* name: 3,7-dimethyl-9-methoxy-12-oxo-1,2,4,5,-6,7-hexahydro-2,7-methano-3*H*-3-benzazonine. The term "homobenzomorphan" has been given to this series of derivatives. See ref 2.

(4) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

(5) V. Seidolová and M. Provita, *Collect. Czech. Chem. Commun.*, **32**, 2826 (1967).

(6) M. E. Kuehne, *J. Amer. Chem. Soc.*, **83**, 1492 (1961).

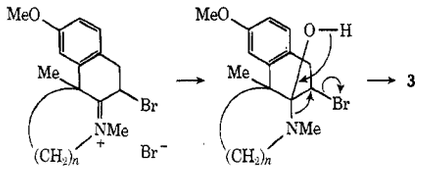
(7) The reductive removal of halogen has been reported in the addition of Grignard reagents to α-bromo iminium salts. See A. Kirrmann, E. Elkik, and P. Vaudescal, *C. R. Acad. Sci., Ser. C*, **262**, 1268 (1966).

(8) M. E. Kuehne in "Enamines; Synthesis, Structure and Reactions," A. G. Cook, Ed., Marcel Dekker, New York and London, 1969, p 415.

no reports have appeared on this sort of bromo enamine rearrangement.

A possible mechanism of the present reaction may be represented by the sequence of reactions shown in Scheme II.

SCHEME II



8 A

Attack of OH^- to the initially formed bromo iminium bromide **8** would give intermediate A, which may undergo, presumably in a concerted manner, rearrangement to **3**.[9]

Experimental Section[10]

1-[3-(*N*-Carbethoxy-*N*-methylamino)propyl]-7-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone (6a).—A solution of **5a**[2] (3.84 g) in benzene (20 ml) was added to a solution of ethyl chloroformate (4.55 g) in benzene (20 ml) at room temperature. The mixture was refluxed for 2 hr, washed with 5% HCl and then with water, dried, and evaporated. The residue was distilled to give **6a** (4.2 g, 90%): bp 185° (0.5 mm); ir (liquid) 1700 cm^{-1}; nmr δ 1.38 (s, 3, CCH_3), 1.19 (t, 3, J = 7 Hz, CH_2CH_3), 2.72 (s, 3, NCH_3), 3.79 (s, 3, OCH_3), 4.16 (q, 2, J = 7 Hz, OCH_2).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.21; H, 7.89; N, 3.99.

1-[2-(*N*-Carbethoxy-*N*-methylamino)ethyl]-7-methoxy-1-methyl-3,4-dihydro-2-(1*H*)-naphthalenone (6b).—This compound was prepared in 83% yield from **5b**[4] in the same manner as that described above: bp 170° (0.2 mm); ir (liquid) 1700 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.41; H, 7.61; N, 4.28.

4,10b-Dimethyl-9-methoxy-1,2,3,4,6,10b-hexahydrobenzo[*f*]-quinoline (7a) Picrate.—A mixture of **6a** (1.67 g), KOH (2 g), and 1-butanol (28 ml) was refluxed for 18 hr and evaporated. The residue was taken up in ether and extracted with 10% HCl. The aqueous layer was made basic with NH_4OH and extracted with ether. Removal of solvent from the dried extracts gave an air-sensitive oil (**7a**), converted into its picrate. Recrystallization from ethanol–acetone gave yellow pillars (1.37 g, 58%), mp 158–160°.

Anal. Calcd for $C_{22}H_{24}N_4O_8$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.92; H, 5.03; N, 12.17.

The free base was regenerated from the picrate (lithium hydroxide–chloroform): ir (liquid) 1655 cm^{-1}; nmr δ 1.40 (s, 3, CCH_3), 2.54 (s, 3, NCH_3), 3.78 (s, 3, OCH_3), 4.75 (t, 1, J = 4 Hz, NC=CH). The **perchlorate** was crystallized from acetone–ether: mp 160–162°; ir 1685 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NO_5Cl$: C, 55.89; H, 6.45; N, 4.08. Found: C, 56.02; H, 6.62; N, 4.11.

3,9b-Dimethyl-8-methoxy-5,9b-dihydrobenz[*e*]indoline (7b) Picrate.—This compound was prepared from **6b** in 56% yield by the method described above: mp 133–136° (from ethanol–acetone).

Anal. Calcd for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.84; N, 12.22. Found: C, 55.14; H, 4.77; N, 12.31.

The free base was highly air-sensitive. The **perchlorate** was crystallized from ethanol–ether: mp 148–150° dec; ir 1683 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}NO_5Cl$: C, 54.62; H, 6.12; N, 4.25. Found: C, 54.58; H, 6.00; N, 4.16.

2′-Methoxy-2,6-dimethyl-10-oxo-7,8-homobenzomorphan (3a).—To a solution of **7a** (regenerated from 2.36 g of the picrate) in CH_2Cl_2 (20 ml) was added Br_2 (0.8 g) in CH_2Cl_2 (10 ml) at −30 to −35° and stirred at the same temperature for 30 min; then the bath was removed to raise the temperature to 0°. Water (10 ml) was added and the mixture was stirred at 5–10° for 2 hr, made basic with 3% aqueous NH_4OH (14 ml), stirred at 5–10° for 2 hr, and then allowed to stand at room temperature overnight. The organic layer was separated and the aqueous phase was extracted with chloroform. The combined organic phase was washed with water, dried, and evaporated to give **3a** (1.05 g, 81%), mp 79–83°. Recrystallization from ethanol gave plates, mp 82–84°, which proved to be identical with an authentic specimen.[2]

2′-Methoxy-2,5-dimethyl-9-oxo-6,7-benzomorphan (3b) Hydrochloride.—To a solution of **7b** (regenerated from 1.83 g of the picrate) in CH_2Cl_2 (20 ml) was added Br_2 (0.64 g) in CH_2Cl_2 (15 ml) at −30 to −35° and stirred at the same temperature for 1 hr.[11] Addition of water (10 ml) and stirring for 2 hr at 5–10° caused precipitation of a crystalline solid (**8b**, *vide infra*). A solution of 3% aqueous NH_4OH (12 ml) was added[12] and the mixture was stirred at 5–10° for 2 hr and then at room temperature overnight. Work-up as above gave an oil which was chromatographed on Al_2O_3 and eluted with benzene. Conversion of the eluate into the hydrochloride and recrystallization from ethanol–ether gave rods (0.675 g, 60%), mp 130–132° (lit.[4] mp 130–132°). The **methobromide** was crystallized from ethanol, mp 216–218°, identical with an authentic sample.[13]

In another run, the precipitated solid was collected from the brominated mixture and recrystallized from acetone–ethanol to give **4-bromo-9b-methyl-8-methoxy-2,4,5,9b-tetrahydro-1*H*-benz[*e*]indole methobromide (8b,** 1.32 g, 83%): mp 124–125°; ir 1673, 3380 cm^{-1} (hydrate H_2O); nmr δ 1.75 (s, 3, CCH_3), 3.87 (s, 3, $=N^+CH_3$), 4.00 (s, 3, OCH_3); *m/e* 309, 307 (M^+), 213 (base).

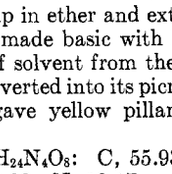
Anal. Calcd for $C_{15}H_{19}NOBr_2 \cdot 0.5H_2O$: C, 45.24; H, 5.06; N, 3.54; Br, 40.13. Found: C, 45.49; H, 4.80; N, 3.42; Br, 39.98.

Treatment of **8b** with 3% aqueous NH_4OH in CH_2Cl_2 gave **3b** in 65% yield.

4-Bromo-3,9b-dimethyl-8-methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole (9) Perchlorate.—To a solution of **8b** (0.2 g) in methanol (13 ml) and water (3 ml) was added sodium borohydride (0.04 g) at 5–10°. The mixture was stirred at room temperature for 2 hr and evaporated. The residue was taken in ether, washed with water, dried, and evaporated. The residue was chromatographed on Al_2O_3 and eluted with benzene. The eluate was converted into the perchlorate and recrystallized from ethanol–ether to give needles (0.115 g, 56%): mp 144–146°; nmr (free base) 1.33 (s, 3, CCH_3), 2.61 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 4.65 (m, 1, CHBr).

Anal. Calcd for $C_{15}H_{21}NO_5ClBr$: C, 43.86; H, 5.15; N, 3.41. Found: C, 44.15; H, 5.21; N, 3.55.

(9) One of the referee of this journal suggests that **3** could also arise from the bromo amino ketone (B), which may be in equilibrium with A.



B

However, the reaction of α-halo ketones with a secondary amine has been recently reported to give β-halo enamines rather than α-amino ketones. See D. Cantacuzène and M. Torieux, *Tetrahedron Lett.*, 4807 (1971).

The higher yield of **3a** than that of **3b**, revealed in this rearrangement, may be also inconsistent with the mechanism involving an intermediate B. For instance, in cyclizing **1a,b** and the related compounds, six-membered amino ketone derivatives have been always obtained more readily than the corresponding seven-membered analogs. See E. L. May, *J. Org. Chem.*, **21**, 223 (1956), and ref 2.

(10) All melting points were determined in an open capillary tube and are uncorrected. Ir spectra were measured in Nujol and nmr spectra were taken in $CDCl_3$ (containing Me_4Si at δ 0.00 as internal standard) at 60 MHz, unless otherwise stated. The organic solutions were dried over sodium sulfate and all evaporations were carried out *in vacuo*.

(11) Treatment of this mixture with triethylamine (at 0° for 2 hr, then at room temperature overnight) gave a multicomponent mixture which did not include **3b** (by tlc).

(12) Direct addition of aqueous NH_4OH to the brominated mixture also gave **3b** in a comparable yield. Thus, it is unnecessary to add water prior to alkalinization.

(13) The authors thank Dr. Everette L. May, National Institutes of Health, for providing us with the sample of **3b** methobromide.

Treatment of **9** with 5% aqueous NH_4OH in CH_2Cl_2 at room temperature overnight resulted in a quantitative recovery of the material.

9-Methoxy-4,4a,10b-trimethyl-1,2,3,4,4a,10b-hexahydrobenzo[*f*]quinoline (10) Hydrobromide.—**7a** (regenerated from 2.92 g of the picrate) was brominated as described previously. Evaporation of CH_2Cl_2 at room temperature gave **8a** as an amorphous powder. Ethereal methylmagnesium iodide (100 ml of 0.43 *M*) was added to a suspension of **8a** in ether (70 ml) and refluxed for 15 hr. The cooled mixture was poured into ice–water containing NH_4Cl, basified with NH_4OH, and extracted with ether. Evaporation of the dried extracts gave the residue which was chromatographed over silica gel (80 g) and eluted with chloroform–methanol (95:5). Conversion of the eluate into the hydrobromide and recrystallization from acetone–methanol–ether gave **10** hydrobromide (0.38 g, 18%): mp 254–256° dec; uv max (MeOH) 282 mμ (ε 14,500); nmr (D_2O) 1.39 (s, 3, CCH_3), 1.44 (s, 3, CCH_3), 3.05 (s, 3, N^+CH_3), 3.95 (s, 3, OCH_3), 6.24 (d, 1, J = 10 Hz, C_5H), 6.75 (d, 1, J = 10 Hz, C_6H).

Anal. Calcd for $C_{17}H_{24}NOBr$: C, 60.36; H, 7.15; N, 4.15; Br, 23.66. Found: C, 60.15; H, 7.26; N, 4.09; Br, 23.52.

Elution with chloroform–methanol (9:1) and conversion of the eluate into the hydrochloride gave **9-methoxy-4,4a,10b-trimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (11) hydrochloride** (0.28 g, 13%): mp 227–230° dec; needles from acetone–methanol–ether; ir 3380, 3440 cm^{-1} (hydrate H_2O); nmr (D_2O) 1.37 (s, 3, CCH_3), 1.54 (s, 3, CCH_3), 3.08 (s, 3, N^+CH_3), 4.05 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{26}NOCl \cdot H_2O$: C, 65.15; H, 8.99; N, 4.46. Found: C, 65.41; H, 8.95; N, 4.52.

Reaction of **7a** perchlorate with ethereal methylmagnesium iodide also gave **11** in 40% yield.

Registry No.—**3a**, 28360-42-1; **3b** hydrochloride, 34887-93-9; **6a**, 34887-94-0; **6b**, 34887-95-1; **7a**, 34887-96-2; **7a** picrate, 34887-97-3; **7a** perchlorate, 34917-95-8; **7b** picrate, 34887-98-4; **7b** perchlorate, 34887-99-5; **8b**, 34887-61-1; **9** perchlorate, 34887-62-2; **10** hydrobromide, 34887-63-3; **11** hydrochloride, 34887-64-4.

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Studies on Heterocyclic Compounds. XI. 1,3-Dipolar Cycloaddition of Benzimidazolium Ylide with Acetylenic Compounds

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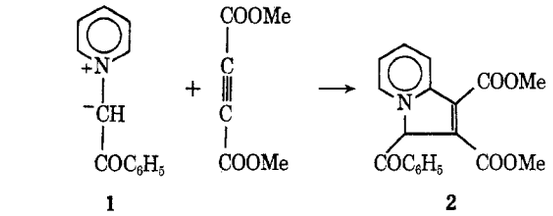
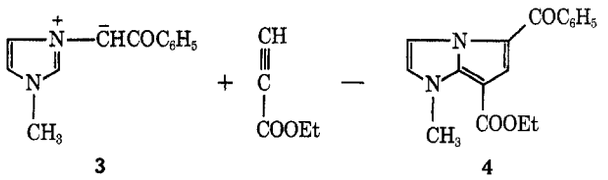
1,3-Dipolar cycloaddition of 3-substituted 1-alkylbenzimidazolium ylides with ethyl propiolate gave 3-substituted 9-alkyl-1-ethoxycarbonylpyrrolo[1,2-*a*]benzimidazoles. Reaction of 1-alkyl-3-phenacylbenzimidazolium ylides with dimethyl acetylenedicarboxylate afforded 4-alkyl-2,3-bis(methoxycarbonyl)-1-phenacylpyrrolo[1,2-*a*]-benzimidazole (**7**) and an open-chain compound (**8**). On the other hand, reaction of 1-alkyl-3-methoxycarbonylmethylbenzimidazolium ylides with dimethyl acetylenedicarboxylate gave 4-alkyl-1,2,3-tris(methoxycarbonyl)-pyrrolo[1,2-*a*]benzimidazole (**9**) and 5-alkyl-3,4-bis(methoxycarbonyl)-1-oxopyrido[1,2-*a*]benzimidazole (**10**).

For the purpose of obtaining potential physiologically active compounds, we synthesized compounds of the tricyclic azole system, such as thiazolo[3,2-*a*]benzimidazoles,[1] thiazolo[2,3-*b*]benzothiazoles,[2] imidazo[2,1-*b*]-benzothiazoles,[3] imidazo[2,1-*b*]benzoxazoles,[4] pyrimido-[1,2-*a*]benzazoles,[5] and imidazo[1,2-*a*]benzimidazoles.[6] In our previous report,[7] 9-alkylamino-2-arylimidazo-[1,2-*a*]benzimidazole showed a strong analgesic activity. We also suggested that pyrrolo[1,2-*a*]benzimidazole systems would have potential physiological activities.

Recently, Boekelheide and coworkers[8] prepared pyrrocoline (**2**) by the reaction of pyridinium ylide (**1**) and methyl acetylenedicarboxylate, and they found that 3-phenacylimidazolium ylide (**3**) reacted with ethyl propiolate to yield 4-benzoyl-6-ethoxycarbonyl-1-methyl-1,3a-diazapentalene[9] (**4**). These facts suggest



1 **2**



3 **4**

that the reaction of benzimidazolium ylide with acetylenic compounds might offer a useful synthesis for pyrrolo[1,2-*a*]benzimidazoles.[10]

Reaction of 3-substituted 1-alkylbenzimidazolium ylides, which were prepared from bromides **5**, with ethyl propiolate gave 1-substituted 4-alkyl-3-ethoxycarbonyl-4*H*-pyrrolo[1,2-*a*]benzimidazoles (**6**) (Chart I). Their structures were confirmed by the ir and nmr spectra. The chemical shift of the C-8 proton in **6a–f** is summarized in Table I, and the values show the para-

(1) H. Ogura, T. Itoh, and Y. Shimada, *Chem. Pharm. Bull.*, **16**, 2167 (1968); H. Ogura, T. Itoh, and K. Kikuchi, *J. Heterocycl. Chem.*, **6**, 797 (1969).

(2) H. Ogura, T. Itoh, M. Ogiwara, and T. Okamoto, *Yakugaku Zasshi*, **89**, 469 (1969).

(3) H. Ogura and T. Itoh, *Chem. Pharm. Bull.*, **18**, 1981 (1970).

(4) H. Ogura, T. Itoh, and S. Sugimoto, *ibid.*, **18**, 2204 (1970).

(5) H. Ogura and M. Kawano, Abstracts of Papers, 91st Annual Meeting of the Pharmaceutical Society of Japan, 1971, p 669.

(6) H. Ogura and T. Itoh, *Kitasato Arch. Exp. Med.*, **42**, 65 (1969).

(7) H. Ogura, M. Kawano, K. Kikuchi, and T. Itoh, Abstracts of Papers, 3rd International Congress of Heterocyclic Chemistry, 1971, p 506.

(8) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **32**, 2062 (1967).

(9) V. Boekelheide and N. A. Fedoruk, *J. Amer. Chem. Soc.*, **90**, 3830 (1968).

(10) H. Ogura, T. Itoh, K. Kikuchi, and H. Sekine, Abstracts of Papers, 91st Annual Meeting of the Pharmaceutical Society of Japan, 1971, p 670.