Synthesis and Amebicidal Activities of Some 1′,2′-Secoemetine Derivatives

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A novel, general method is reported for converting benzindolizines and benzquinolizines of types **21** and **22** to the corresponding benzazonines and benzazecines of types **29** and **30**. It involves quaternization with 3,3-ethylenedioxy-1-*p*-toluenesulfonate, scission of the bridgehead carbon–nitrogen bonds in the resulting salts with lithium in liquid ammonia, and hydrolysis of the labile 3,3-ethylenedioxybutyl groups. Application of the method to 2-benzyloxycarbonylemetine and 2-acetylemetine gives 1′,2′-secoemetine (**7**) and 2-acetyl-1′,2′-secoemetine (**8**), respectively. Compound **7** is less efficiently prepared through lithium–ammonia reduction of 2-*p*-methoxybenzoylemetine methiodide (**2**) and von Braun degradation of the intermediate 2-*p*-methoxybenzoyl-1′,2′-secoemetine (**9**). Compound **8** is less efficiently prepared through lithium–ammonia reduction of 2-acetylemetine methiodide (**1**) and von Braun degradation of the resulting 1′,2′-secoemetine (**6**). Amebicidal potencies are reported for the secoemetines **6–8**, **17**, and **18**.

In a previous paper[2] we described the selective reduction of 2-acetylemetine methiodide (**1**) by lithium and 1-methoxy-2-propanol in liquid ammonia to the 1′,2′-secoemetine (**6**)[3] and have reported that, in preliminary *in vitro* tests conducted elsewhere, **6** showed the same order of amebicidal activity as emetine itself. We now communicate studies on the synthesis and amebicidal activity of several related compounds which were undertaken in the hope of finding a highly potent amebicidal secoemetine with a lower toxicity[4] than the parent alkaloid.

The activity of **6** suggested the preparation of the analog **7** which is even more closely related to emetine. We believed that **7** would be best synthesized from emetine by a process involving, successively, acylation at N-2, quaternization at N-2′, metal–ammonia cleavage of the 1′,2′ bond, and removal of any group(s) remaining attached to nitrogen. The initial acylation is needed to restrict the formation of cationic nitrogen to N-2′ in the subsequent quaternization, and the successful use of the reaction sequence requires the selection of appropriate acylating and alkylating groups. Since our earlier work[2] had demonstrated the conversion of the N-methylbenzazecine (**25**) to its imino analog (**26**), and since no undue difficulty was expected in hydrolyzing the N-acetyl group, we at first intended to make **7** *via* **6** and **8**. However, preliminary experiments showed the N-acetyl group in **6** to be markedly resistant to hydrolysis even under strongly acidic or basic conditions, and so a potentially more labile acylating group was sought. *p*-Methoxybenzoyl appeared satisfactory on observing that N-*p*-methoxybenzoylemetine methiodide (**2**) was converted in high yield by lithium and 1-methoxy-2-propanol in liquid ammonia to the seco derivative **10**. The *p*-methoxybenzoyl group was presumably removed through the reduction of **2** to the α,α-hydroxylamine (**11**) which subsequently decomposed to **10** and *p*-methoxybenzaldehyde.[5] Notably, in the analogous transformation of **1** to **6**, the N-acetyl group remained intact.[1] The benzoyl group was less satisfactory than *p*-methoxybenzoyl, since, although lithium–ammonia reduction apparently resulted in the formation of **10**, the cleavage of the benzoyl group was incomplete, and the mixture of bases **10** and **12** was accompanied by several other ill-defined and difficultly separable products.

Combination of the *p*-methoxybenzoyl acylating group with the methyl quaternizing group in the proposed reaction sequence permitted the first synthesis of **7** to be carried out. The base **10**, formed by lithium–ammonia reduction of **2**, was reacylated with *p*-methoxybenzoyl chloride to ensure exclusive attack at N-2′ in the ensuing von Braun degradation with cyanogen bromide. The degradation product contained the desired cyanamide **13**, from its subsequent conversion to **7** together with other components formed by scission of the benzazecine ring. The impurities were partially removed by refluxing with a large excess of diethylamine and extracting the resulting bases with hydrochloric acid. Reduction of the neutral product with lithium and ethanol in liquid ammonia then gave a mixture separated by preparative thin layer chromatography into the required **7** and an oily component. The transformation of the cyanamido group in **13** to the amino group in **7** may occur through direct cleavage of cyanide anion from nitrogen or, more probably, by reduction to the labile α,α-diamine **14**, which undergoes decomposition to **7** and formaldehyde during work-up. The proton nmr spectrum of the accompanying product displays signals attributable to a styrenoid vinyl group which are replaced after catalytic hydrogenation by signals consistent with an ethyl group attached to a benzene ring (see Experimental Section). These data are in accord with structure **19**, formed by von Braun cleavage at the 2′,3′ position, the styrenoid double bond having survived the final metal–ammonia reduction.

The inefficiency of the foregoing synthesis of **7** (7.5% over-all from emetine), which is mainly due to the lack of selectivity of the von Braun degradation, prompted a search for an alternate, more labile, quaternizing group. Initially, our attention was

(1) Postal address: P. O. Box 8299, Philadelphia, Pa. 19101.

(2) D. Herbst, R. Rees, G. A. Hughes, and H. Smith, *J. Med. Chem.*, **9**, 864 (1966).

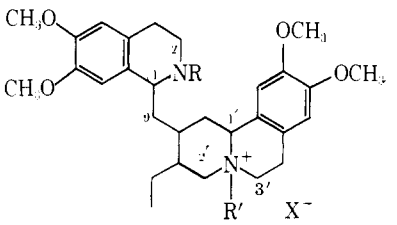
(3) We adopt the emetine numbering system previously used by E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, *J. Am. Chem. Soc.*, **79**, 4817 (1957).

(4) E. F. Elslager in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 855, has noted the toxic side effects of emetine.

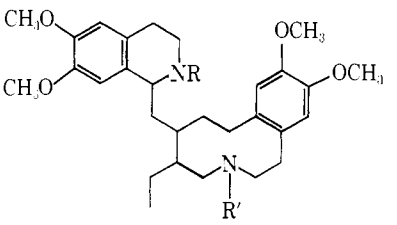
(5) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., New York, N. Y., 1963, pp 219, 220, and references therein cited.

directed to 3-hydroxybutyl by the report[6] that this grouping is readily detached from nitrogen by Oppenauer oxidation followed by elimination of methyl vinyl ketone from the resulting β-amino ketone. However, in preliminary experiments we found that quaternization of N-acetylemetine with 3-hydroxybutyl bromide was accompanied by formation of the corresponding hydrobromide salt, presumably from the hydrogen bromide produced by decomposition of the unstable bromide. This salt was formed even with excess alkylating agent and was difficult to separate from the required quaternary salt. Therefore, we directed our attention to the 3,3-ethylenedioxybutyl group as introduced into quaternary salts through the tosylate **20**,[7] and chose to investigate its utility in the model benzazonine and benzazecine systems **21** and **22**,[8] respectively. The novel tosylate is readily prepared from ethyl 3,3-ethylenedioxybutyrate[9] by reduction with lithium aluminum hydride followed by tosylation of the resulting alcohol in pyridine at 0°. It is somewhat unstable at room temperature, although quite stable for extended periods (>2 months) at −10°. Although considerably less reactive as a quaternizing reagent than 3-hydroxybutyl bromide, the tosylate formed moderate yields (50–85%) of the tosylate salts **23** and **24** from the corresponding bases in refluxing acetonitrile. Generally, lower yields were obtained by quaternizing in ethyl acetate at 130° under pressure. Reduction of these salts with lithium and 1-methoxy-2-propanol in liquid ammonia gave the bases **27** and **28**, and acid hydrolysis of each followed by refluxing with hydrazine sulfate afforded **29** and **30** from the corresponding tricyclic bases in yields of 60 and 25%, respectively. Combination of 3,3-ethylenedioxybutyl as the alkylating group with benzyloxycarbonyl as the acylating group then provided an efficient route from emetine to **7**. Thus, the salt **4**, obtained by quaternizing the noncrystalline N-benzyloxycarbonylemetine, on reduction with lithium–ammonia, gave the base **15**, cleavage of the bridgehead bond being accompanied by scission of the benzyloxy group,[10] and final removal of the N-2′ group as before afforded the desired **7** in 30% over-all yield from emetine. The salt **5** from N-acetylemetine was transformed by an analogous procedure *via* **16** to **8**, the carboxamide group again surviving the metal–ammonia reduction step. To complete a series for antiamebic screening, **6** and **8** were reduced with lithium aluminum hydride to the N-ethyl compounds **17** and **18**, respectively. The latter was also prepared, although less satisfactorily, through the lithium aluminum hydride reduction of the crude product, presumably the corresponding N-2′-cyanamide, from the von Braun degradation of **6**.

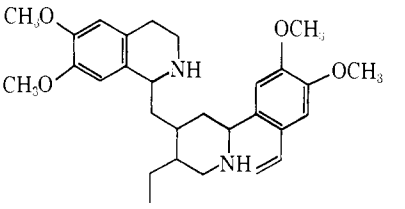
Amebicidal Activity.—Compounds **6**, **8**, **17**, and **18** were screened for amebicidal activity as their hydrochloride salts and **7** as its hydriodide salt in a test[11] involving the incubation of polybacteria and trophozoites of *Entamoeba histolytica* NIH 200 in the aqueous phase of a modified Boeck–Drbohlav biphasic medium containing the drug. The minimum inhibitory concentration for each was *ca.* 1 mg/ml compared to values of 1.95–3.90 μg/ml found for emetine hydrochloride



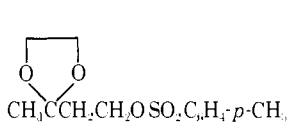
	R	R′	X
1	CH_3CO	CH_3	I
2	p-$CH_3OC_6H_4CO$	CH_3	I
3	C_6H_5CO	CH_3	I
4	$C_6H_5CH_2OCO$	$CH_3C(OCH_2)_2CH_2CH_2$	p-$CH_3C_6H_4SO_3$
5	CH_3CO	$CH_3C(OCH_2)_2CH_2CH_2$	p-$CH_3C_6H_4SO_3$



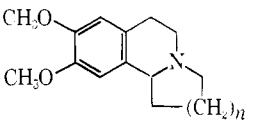
	R	R′
6	CH_3CO	CH_3
7	H	H
8	CH_3CO	H
9	p-$CH_3OC_6H_4CO$	CH_3
10	H	CH_3
11	p-$CH_3OC_6H_4CHOH$	CH_3
12	C_6H_5CO	CH_3
13	p-$CH_3OC_6H_4CO$	CN
14	p-$CH_3OC_6H_4CO$	CH_2NH_2
15	H	$CH_3C(OCH_2)_2CH_2CH_2$
16	CH_3CO	$CH_3C(OCH_2)_2CH_2CH_2$
17	C_2H_5	CH_3
18	C_2H_5	H



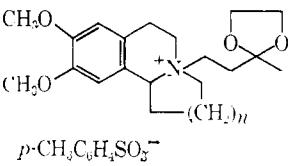
19



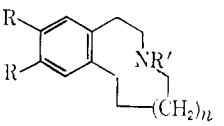
20



21, n = 1
22, n = 2



23, n = 1
24, n = 2



	R	R′	n
25	H	CH_3	2
26	H	H	2
27	CH_3O	$CH_3C(OCH_2)_2CH_2CH_2$	1
28	CH_3O	$CH_3C(OCH_2)_2CH_2CH_2$	2
29	CH_3O	H	1
30	CH_3O	H	2

(6) D. E. Clark, R. F. K. Meredith, A. C. Ritchie, and T. Walker, *J. Chem. Soc.*, 2490 (1962).

(7) R. E. Thornton and H. Smith, unpublished work; R. E. Thornton, Ph.D. Thesis, Manchester, 1957.

(8) R. Child and F. Lee Pyman, *J. Chem. Soc.*, 36 (1931).

(9) E. J. Salmi, *Ber.*, **71**, 1803 (1938).

(10) H. Smith, ref 5, p 187, and references therein cited.

(11) P. E. Thompson, D. A. McCarthy, A. Bayles, J. W. Reinertson, and A. R. Cook, *Antibiot. Chemotherapy*, **6**, 337 (1956).

under parallel conditions.[12] Thus, although **6** and its relatives can produce the same order of activity as emetine, *i.e.*, 100% kill at the appropriate dosage, their amebicidal potency is approximately 0.25% that of the parent alkaloid.

Experimental Section

All evaporations were under reduced pressure. Melting points were taken on a Kofler block under microscopic magnification or in capillary tubes using the Thomas–Hoover apparatus and are uncorrected. Pmr spectra were measured with a Varian Associates A-60 spectrometer on 10–15% solutions in $CDCl_3$ containing tetramethylsilane as internal reference standard. Chemical shifts are measured in δ units measured downfield from the reference and coupling constants, J, in cps. The former should be accurate to ± 0.01 ppm, and the latter to 0.5 cps. Thin layer chromatography was conducted on silica gel plates with rice starch as binder and visualization of the chromatograms with a freshly prepared modified Dragendorff reagent.[13]

2-*p*-Methoxybenzoylemetine.—Emetine (from the dihydrochloride, 25 g) in ethyl acetate (350 ml) was shaken for 10 min under H_2O cooling with 20% aqueous NaOH (150 ml) and *p*-methoxybenzoyl chloride (20 g). Recrystallization of the product from ether gave the amide (18 g), mp 138–144°; analytical sample (from ether), mp 136–142°.

Anal. Calcd for $C_{37}H_{46}N_2O_6$: C, 72.28; H, 7.54; N, 4.56. Found: C, 72.57; H, 7.45; N, 4.69.

2-*p*-Methoxybenzoyl-2′-methyl-1′,2′-secoemetine (9).—The foregoing amide (16 g) was kept for 4 hr at room temperature with MeI (20 ml) in C_6H_6 (150 ml). The resulting methiodide **2** (19 g), mp 210–214°, after reduction with Li (0.5 g) and 1-methoxy-2-propanol (15.5 g) in liquid NH_3 (3 l.) gave the oily base **10** (11.5 g) (no infrared amide absorption), which was *p*-methoxybenzoylated as before. Two recrystallizations of the product from acetone–ether gave the secoemetine (6.6 g): mp 188–193°; nmr, three-proton ill-resolved triplet δ 0.96 ($C-C_2H_5$), broad three-proton singlet δ 2.27 ($N-CH_3$), 15-proton series of singlets δ 3.76, 3.86, 3.89, 3.91 (OCH_3), multiplets at δ 5.10 and 5.85 totalling one proton (C-1 H[14]), eight-proton multiplet δ 6.40–7.50 (aromatic H).

Anal. Calcd for $C_{38}H_{50}N_2O_6$: C, 72.35; H, 7.99; N, 4.44. Found: C, 71.65; H, 7.74; N, 4.22.

3,3-Ethylenedioxy-1-*p*-toluenesulfonate (20).—Ethyl 3,3-ethylenedioxybutyrate[9] (85 g) in tetrahydrofuran (THF, 200 ml) was added with stirring under N_2 to a suspension of $LiAlH_4$ (14 g) in THF (200 ml) so that the solvent refluxed gently; refluxing was continued for 3 hr. To the cooled mixture was added, successively, H_2O (8 ml), 20% aqueous NaOH (6 ml), and H_2O (25 ml). The resulting 3,3-ethylenedioxy-1-butanol (34.8 g), bp 89° (10 mm), showed no infrared C=O absorption. The alcohol (6 g) was stirred for 5 hr under N_2 at 0° (bath) with *p*-toluenesulfonyl chloride (10.8 g) in pyridine (30 ml). Ice was added, and the mixture was stirred for 30 min and extracted with ether. Evaporation of the washed and dried extract and washing of the residue with hexane gave **20** as a thick oil, λ_{max}^{film} 6.25, 7.37, 8.49 μ. This material was sufficiently pure for further use. The analytical sample was dried for 8 hr at room temperature *in vacuo*.

Anal. Calcd for $C_{13}H_{18}O_5S$: C, 54.54; H, 6.34; S, 11.17. Found: C, 54.58; H, 6.32; S, 11.43.

1,2,3,5,6,10b-Hexahydro-8,9-dimethoxy-4-(3,3-ethylenedioxybutyl)benzo[*g*]indolizium Tosylate (23).—Compounds **21**[8] (14.2 g) and **20** (20.6 g) were refluxed for 40 hr under N_2 with CH_3CN (48 ml). The cooled mixture was added to ether, and the resulting solid was stirred for 2 hr with acetone containing a trace of pyridine to give the salt (30 g), mp 157–158°. The analytical sample had mp 157–158° (from CH_2Cl_2–acetone containing a trace of pyridine).

Anal. Calcd for $C_{27}H_{35}NO_7S$: C, 62.41; H, 7.18; N, 2.70; S, 6.16. Found: C, 62.33; H, 7.15; N, 2.61; S, 6.2.

1,3,4,6,7,11b-Hexahydro-5-(3,3-ethylenedioxybutyl)-9,10-dimethoxy-2H-benzo[*a*]quinolizium *p*-Toluenesulfonate (24). Compound **22**[8] (6.1 g) was kept for 30 hr with **20** (8.5 g) and ethyl acetate (20 ml) at 132° in a Parr bomb. The mixture was evaporated and the residue on trituration with ether followed by recrystallization of the product from Me_2CO gave the salt (5.38 g), mp 153–155.5°. A second crop (0.3 g), mp 153–154°, was obtained by concentrating the mother liquors. The same salt was obtained in 50% yield when the reaction was carried out in CH_3CN as for **23**.

Anal. Calcd for $C_{35}H_{39}NO_7S$: C, 63.02; H, 7.37; N, 2.63; S, 6.01. Found: C, 63.16; H, 7.07; N, 2.90; S, 5.8.

1,2,3,4,5,6,7,8-Octahydro-10,11-dimethoxy-3-benzazecine (30) Hydrochloride. Reduction of **24** (4.25 g) with Li (123 mg) and 1-methoxy-2-propanol (0.86 ml) in liquid NH_3 (4 l.) afforded **28** as an oil (3.04 g) [nmr, three-proton singlet δ 1.22 (ethylenedioxybutyl CH_3), four-proton singlet δ 3.87 (ketal H)] which was stirred under N_2 at room temperature overnight in CH_3OH–1 *N* HCl–H_2O (60:30:30 ml). The oily product (2.2 g), largely 3-(3-oxobutyl)-1,2,3,4,5,6,7,8-octahydro-10,11-dimethoxy-3-benzazecine [nmr, three-proton singlet δ 1.87 ($COCH_3$), four-proton singlet δ 2.72 (oxobutyl CH_2)] was dissolved in refluxing MeOH–H_2O (60:120 ml) containing hydrazine sulfate (5 g), enough MeOH was distilled off to raise the boiling point to 100°, and the mixture was refluxed for 3 hr. The cooled mixture was basified with concentrated aqueous NH_4OH and extracted with $CHCl_3$. Evaporation of the washed and dried extract gave a residue which was percolated rapidly in ether through basic Al_2O_3 (12 g) to give **30** (1.73 g), mp 73–76°, unstable to air. The hydrochloride had mp 120–125° (from acetone–ether).

Anal. Calcd for $C_{15}H_{24}ClNO_2 \cdot 0.25H_2O$: C, 62.06; H, 8.51; Cl, 12.26; N, 4.82. Found: C, 62.00; H, 8.33; Cl, 12.00; N, 4.55.

2,3,4,5,6,7-Hexahydro-9,10-dimethoxy-1H-3-benzazonine Hydrochloride.—Compound **23** (12.5 g) was converted *via* crude **27** (8 g) into the base **29** (4 g) by the procedure used for converting **24** to **30**. The hydrochloride of **29** had mp 182–184° (from acetone–$CHCl_3$).

Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 62.00; H, 8.18; Cl, 13.08; N, 5.17. Found: C, 61.71; H, 7.92; Cl, 13.20; N, 4.85.

1′,2′-Secoemetine Hydroiodide. A.—Compound **9** (3.8 g) was kept overnight at room temperature with BrCN (3.8 g) in THF (250 ml). Ethyl acetate was added, and the mixture was washed with 2 *N* HCl and H_2O. The neutral product was refluxed for 4 hr with C_6H_6–Et_2NH (200:100 ml), and the cooled solution was washed with 2 *N* HCl and H_2O. The neutral, oily product was reduced with Li (0.5 g) and 1-methoxy-2-propanol (2 g) in liquid NH_3 (1 l.). The crude product in $CHCl_3$ was extracted into 2 *N* HCl, and the acid solution was basified to yield an oil (1.6 g) which was separated by preparative tlc on silica gel plates under irrigation with NH_3-saturated $CHCl_3$ into the oily base **7** (R_f 0.47, 0.75 g) and a second basic fraction (R_f 0.87, 0.43 g). The amorphous hydrochloride of **7** was converted by aqueous KI to the hydroiodide, mp 190–195° (from H_2O).

Anal. Calcd for $C_{29}H_{44}I_2N_2O_4 \cdot H_2O$: C, 46.04; H, 6.13; I, 33.55; N, 3.70. Found: C, 46.02; H, 6.01; I, 33.80; N, 3.30.

The second basic fraction (120 mg), presumably **19** [nmr, three-proton ill-resolved triplet δ 0.92 ($C-C_2H_5$), nine-proton multiplet δ 3.83 (OCH_3), three-proton singlet δ 4.02 (OCH_3), two-proton multiplet δ 5.50–6.00 ($C=CH_2$), five-proton multiplet δ 6.50–7.30 (four aromatic and one styrenoid H)] was shaken for 2.5 hr at atmospheric pressure under hydrogen in acetic acid containing Pt (70 mg) to give an amorphous product (95 mg): nmr, three-proton triplet δ 0.96 ($C-C_2H_5$), three-proton triplet δ 1.25 (aromatic C_2H_5), nine-proton multiplet δ 3.80 (OCH_3); three-proton singlet δ 4.05 (OCH_3), four-proton multiplet δ 6.40–7.40 (aromatic H).

B.—Emetine dihydrochloride (6 g) was stirred at room temperature for 45 min in ether (250 ml) and saturated aqueous $NaHCO_3$ (250 ml) containing benzyloxycarbonyl chloride (2.3 g). The ether layer was separated and extracted (2 *N* H_2SO_4, H_2O). The resulting oily precipitate and the aqueous solution were washed with ether, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the washed and dried extract and percolation of the residue in benzene–ether (1:2) through basic Al_2O_3 gave benzyloxycarbonylemetine as an oil (6 g), $\lambda_{max}^{5.92}$ 5.92 μ. This carbamate (10 g) was refluxed under N_2 for 42 hr in CH_3CN (12 ml) containing **20** (5 g). Addition of the mixture to ether precipitated the tosylate **4** as an amorphous powder (6 g). Reduction of the tosylate (4.9 g) with Li (0.22 g)

(12) We thank Drs. G. Warren and S. Rosenman, Microbiology Department, Wyeth Laboratories Inc., for these data.

(13) H. Schriftman, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 111 (1959).

(14) G. Frankel, M. P. Cava, and D. R. Dalton, *J. Am. Chem. Soc.*, **89**, 329 (1967), have attributed similar results with 2-acetyl-1-benzyltetrahydroisoquinolines to an equilibrium involving two conformers.

and 1-methoxy-2-propanol (2.3 ml) in liquid NH_3 (2 l.) gave **15** as an oil (3.6 g) which was stirred overnight at room temperature in 5.5 *N* HCl–MeOH (60:60 ml). The ketonic product was decomposed with hydrazine sulfate as before to give the base **7** as a yellow oil (2.08 g) giving a hydrochloride and hydriodide identical with those obtained as in A.

2-Acetyl-1′,2′-secoemetine (8).—2-Acetylemetine (11 g) was refluxed for 30 hr under N_2 with **20** (11 g) in MeCN (40 ml), and the cooled mixture was added to ether to give the salt **5** as a yellow powder (7 g). The salt (6.2 g) was reduced with Li (129 mg) and 1-methoxy-2-propanol (0.92 ml) in liquid NH_3 (2 l.). The oily ketal **16** was hydrolyzed with methanolic HCl and the resulting ketone decomposed with aqueous methanolic hydrazine sulfate as before. The product was chromatographed on Al_2O_3, elution with $CHCl_3$ giving the secoemetine **8** (8 g), mp 140–142°. The analytical sample had mp 140–141.5° (from ether).

Anal. Calcd for $C_{31}H_{44}N_2O_5$: C, 70.96; H, 8.45; N, 5.34. Found: C, 71.23; H, 8.69; N, 5.49.

The base formed an amorphous **hydrochloride**, mp 146–152°.

Anal. Calcd for $C_{31}H_{45}ClN_2O_5 \cdot 1.5H_2O$: C, 63.02; H, 8.21; N, 4.76. Found: C, 63.27; H, 8.02; N, 4.92.

2-Ethyl-2′-methyl-1′,2′-secoemetine (17).—Compound **6** (5 g) was refluxed with $LiAlH_4$ (5 g) in THF (350 ml) for 3 hr, and the cooled mixture was added to crushed ice. Recrystallization of the product from hexane gave **17** (2.8 g), mp 95–99°. The analytical sample had mp 99–100.5° (from hexane).

Anal. Calcd for $C_{32}H_{48}N_2O_4$: C, 73.24; H, 9.22; N, 5.34. Found: C, 73.27; H, 9.59; N, 5.66.

The base formed an amorphous **dihydrochloride**.

Anal. Calcd for $C_{32}H_{50}Cl_2N_2O_4 \cdot 1.5H_2O$: C, 61.50; H, 8.56; Cl, 11.40; N, 4.50. Found: C, 61.54; H, 8.76; Cl, 12.1; N, 4.61.

2-Ethyl-1′,2′-secoemetine (18). A.—Compound **6** (2 g) was kept with BrCN (2.4 g) in ether–benzene (120:40 ml) for 18 hr. The product was worked up and purified as for the analogous reaction with **9** to give a neutral oil (1.8 g) which with $LiAlH_4$ (2 g) was refluxed for 16 hr in THF–ether (50:50 ml). Recrystallization of the product from ether–hexane gave **18** (0.7 g), mp 146–148°.

Anal. Calcd for $C_{31}H_{46}N_2O_4$: C, 72.90; H, 9.08; N, 5.49. Found: C, 72.59; H, 9.01; N, 5.33.

The base formed an amorphous **dihydrochloride**.

Anal. Calcd for $C_{31}H_{48}Cl_2N_2O_4 \cdot H_2O$: C, 61.89; H, 8.38; Cl, 11.79; N, 4.66. Found: C, 61.93; H, 8.55; Cl, 11.65; N, 4.66.

B.—Reduction of **8** (2.8 g) with $LiAlH_4$ (4 g) in ether–THF (1:1, 400 ml) gave **18** (1.4 g), mp 153–154° (from hexane), undepressed by material prepared as in A.

Chemical and Biological Properties of Some Aminomethyl-2-phenylcyclopropane Derivatives. Pharmacological Comparison with Tranylcypromine

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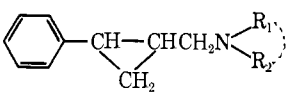
The synthesis of a series of aminomethyl-2-phenylcyclopropane derivatives is described. Unlike tranylcypromine in which the nitrogen atom is attached directly to the cyclopropane ring, none of the amino derivatives tested inhibited the activity of monoamine oxidase (MAO). However, the compounds appeared to retain marked antidepressant activity and interesting sympathomimetic properties. The intermediate amido derivatives were also examined.

One of the early studies about the biological properties of molecules containing small rings was by Burger and Yost[1] on cyclopropane compounds. Following the suggestion that "alicyclic residues might confer desirable pharmacological properties if introduced into compounds containing an auxopharm group"[2] Burger chose the cyclopropane ring as an alicyclic residue for incorporation in the phenethyl group. The compound, 2-phenylcyclopropylamine, originally examined as a sympathomimetic agent, later proved to be an interesting psychotherapeutic drug and a potent MAO inhibitor. Nevertheless, there is no evidence that the clinical antidepressant activity is related to the MAO-inhibitory action. In approaching this interesting question we found that a compound related to tranylcypromine, *i.e.*, *trans*-2-phenylcyclopropylmethylenamine, exhibited actions similar to those of tyramine (motor excitatory effects, hypertensive and anorexic activities). This compound had been shown to exhibit no MAO-inhibitory action,[3] but it serves indeed as substrate of the enzyme.

Therefore we wished to study whether in such a structure retaining sympathomimetic action but lacking MAO-inhibitory activity one would encounter tranylcypromine-like antidepressant action. For this purpose we prepared a series of phenylcyclopropane derivatives having the structural formula I where R_1 and R_2 represent hydrogen, alkyl, alkylene, cycloalkyl, or arylalkyl radicals as specified in Tables III and IV.

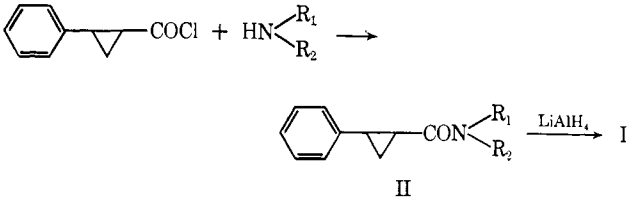


I

Such compounds exist as *cis* or *trans* isomers; most of the substances prepared by us are the *trans* isomers, but some *cis* compounds have been synthesized in order to examine whether any difference of biological activity is detectable for the two different configurations. We generally synthesized the products I according to Scheme I.

The amide derivatives II (Tables I and II) were obtained from the reaction of the acid chloride or by treating ethyl 2-phenylcyclopropanecarboxylate with

SCHEME I



II

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