temperature and then poured into water. It was extracted with chloroform, washed with 10% hydrochloric acid and dried (magnesium sulfate). On evaporating the solvent a brown oily substance was left which could not be crystallized. It was heated for 0.5 hr. with a mixture of glacial acetic acid (10 cc.) and hydrochloric acid (1 cc.). The mixture was poured into a large volume of water which resulted in the separation of a faintly pink solid. On crystallization from ethanol it gave colorless needles, m.p. 153–154°. The ester (0.5 g.) in alcohol was refluxed for 4 hr. with excess of 5% aqueous sodium carbonate. After evaporation of alcohol the solution was cooled and acidified. The precipitate obtained was taken up in ether and thoroughly washed with an aqueous solution of sodium bicarbonate. The bicarbonate extract on acidification gave a solid product which on repeated crystallization from methanol separated into yellow shining needles, m.p. 220–221°. The ethereal layer on evaporation left a small quantity of unchanged XI. The carboxyisoflavone was decarboxylated in the usual manner by heating at 235°. On subsequent workup it gave a solid which on crystallization from methanol separated into colorless shining needles, m.p. 158–160°. It showed no depression in melting point with the 5,7-dimethoxy-8-methylisoflavone (X a) synthesized by either of the methods (a) and (b).

5,7-Dihydroxy-6-methyl isoflavone (IX b). The carbethoxyisoflavone, m.p. 243–244°, (1.2 g.) on hydrolysis in the usual manner gave a product which on crystallization from dilute methanol separated into light yellow aggregates of needles (0.5 g.) m.p. 281–282° dec. It gave a blackish green ferric chloride reaction.

Anal. Calcd. for $C_{17}H_{12}O_6$: C, 65.38; H, 3.84. Found: C, 65.54; H, 3.91.

The carboxyisoflavone was decarboxylated in portions (*ca.* 50 mg.) at 295° exactly as described earlier. The product on crystallization from ethyl acetate gave rectangular plates m.p. 225–227°. It gave a positive test of isoflavone with sodium amalgam followed by acidification. It was characterized as 5,7-dihydroxy-6-methyl isoflavone (IX b).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.48. Found: C, 71.38; H, 4.61.

5-Hydroxy-7-methoxy-6-methylisoflavone (XII). 5,7-Dihydroxy-6-methylisoflavone (IX b) (0.3 g.) in dry acetone (50 cc.) was heated under reflux with methyl sulfate (1 mole) and anhydrous potassium carbonate (1 g.) for 8 hr. The product on the usual work up separated in quantitative yield from a large volume of methanol as light yellow needles changing into clusters of fine needles at 150° and finally melting at 170–172°. It gave a bluish green ferric chloride reaction in alcohol.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.29; H, 4.76.

5,7-Dimethoxy-6-methylisoflavone (X b). (a) The above isoflavone (XII) (0.2 g.) on further methylation with methyl sulfate (large excess)– potassium carbonate–acetone for 60 hr. gave a quantitative yield of 5,7-dimethoxy-6-methylisoflavone (X b) as colorless needles, m.p. 149–150°, (from dilute methanol.) It gave no color with alcoholic ferric chloride and a pink color with sodium amalgam.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 73.01; H, 5.29.

(b) Benzyl 2,4,6-trihydroxyphenyl ketone (XIV)[12] (2.6 g.) on ethoxalylation gave 2-carbethoxy-5,7-dihydroxyisoflavone (2.45 g. 70%; *cf.* 45% Baker *et al.*[10]) as light yellow needles, m.p. 230°. The carbethoxyisoflavone on work-up according to Baker *et al.*[10] gave 5,7-dihydroxyisoflavone (XIII) as plates, m.p. 195–196°.

5,7-Dihydroxyisoflavone (XIII), (0.45 g.) in methanol (25 cc.) containing dissolved sodium (0.7 g.) and methyl iodide (3.5 cc.) was refluxed for 15 hr. The product after removing the solvent under reduced pressure was treated with water and 2*N* hydrochloric acid. The precipitate on washing with water separated from a large volume of methanol in light yellow needles (80 mg.) changing into clusters of fine needles at 150° and finally melting at 170–172°. No depression in melting point was noted on admixture with 5-hydroxy-7-methoxy-6-methylisoflavone (XII) obtained earlier. It gave a bluish green ferric reaction in alcohol.

Further methylation for 60 hr. with methyl sulfate (large excess) potassium carbonate–acetone gave a quantitative yield of 5,7-dimethoxy-6-methylisoflavone (X b), m.p. and mixed m.p. with the compound obtained earlier 149–150°. It gave no coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41. Found: C, 72.73; H, 5.52.

ALIGARH, INDIA

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[12] G. G. Badcock, G. W. K. Cavill, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 2961 (1950).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Structures Related to Morphine. XX.[1] Stevens Reaction in the Synthesis of 5-Ethyl-2′-hydroxy-2-methyl-(or phenethyl)-6,7-benzomorphan

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The Stevens reaction has been applied to the synthesis of 5-ethyl-2′-hydroxy-2-methyl (and -phenethyl)-6,7-benzomorphan (V). The 2-methyl compound (Va) was converted to the 2-phenethyl analog (Vb) and to 1-ethyl-7-methoxynaphthalene by standard reactions.

Previously we reported the synthesis and analgesic activity of 2′-hydroxy-2,5-dimethyl-6,7-benzomorphan (Xa)[3] and the 2-phenethyl analog (Xb).[4] Although the former was only a little more active than codeine, like other members of this class[1] it had no capacity for suppressing abstinence from morphine in an established addiction in the

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[1] Paper XIX, J. H. Ager and E. L. May, *J. Org. Chem.*, **27**, 245 (1962).

[2] Visiting Scientist from Osaka, Japan.

[3] N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

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

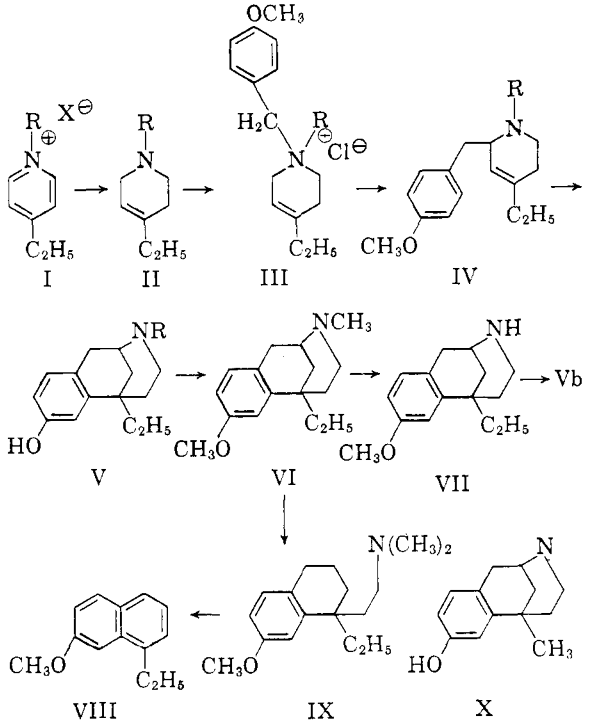
monkey. Furthermore, the 2-phenethyl compound,[4] nearly as powerful an analgesic (in mice) as phenazocine,[5] again had no abstinence suppressing property in monkeys. In view of these favorable results, and as a recent extension[6] of the Stevens rearrangement has provided a more practicable method of preparation of 5-alkyl-2′-hydroxy-2-methyl-6,7-benzomorphans than hitherto[4] published, the synthesis of 5-ethyl homologs (V) was undertaken in the continuing search for safer, more efficacious, pain-relieving agents.

4-Ethyl-1-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridinium chloride (IIIa), prepared in 82% yield by sodium borohydride reduction of 4-ethyl-1-methylpyridinium iodide (Ia) and quaternization of the product (IIa) with *p*-methoxy benzyl chloride in acetone, when treated with a one-molar excess of ethereal phenyllithium, underwent rearrangement yielding principally 4-ethyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine (IVa). The distilled IVa (not otherwise purified or characterized) gave 5-ethyl-2′-hydroxy-2-methyl-6,7-benzomorphan (Va) in 40% over-all yield (based on IIIa) after treatment with 48% hydrobromic acid in the usual way.[5] Similarly, Vb resulted from 4-ethyl-1-phenethylpyridinium bromide (Ib). In this instance the chloride IIIb could not be obtained crystalline but was subjected to rearrangement as an amorphous powder. Invariably, small yields of biphenyl and apparently 1,1-*bis*(*p*-methoxyphenyl)ethane could be isolated from the neutral fraction obtained in the Stevens rearrangement.

Compound Vb could also be obtained from Va by the standard scheme of reactions picture in figure 1.[7] Degradation of Va to 1-ethyl-7-methoxynaphthalene was effected by exhaustive methylation of the Va methyl ether (VI), hydrogenation of the resulting methine, and palladium-charcoal aromatization.

Compound Va (racemate) was equal to morphine in analgesic potency in the mouse,[8] and Vb is ten times more potent, comparable to phenazocine. Each is therefore superior to its 5-methyl counterpart (X).[3,4]

Preliminary data[9] indicate that Va has no morphine-like properties at 2 and 4 mg./kg. in addicted monkeys stabilized on 3 mg./kg. of morphine. The *N*-phenethyl analog, Vb, likewise does not suppress morphine abstinence at 0.5 and 1.0 mg./kg., gives only slight suppression at 2–8 mg./kg., but appears to have complete morphine-like physical dependence capacity with strong stimulant action at 15 mg./kg. Thus Vb is rated intermediate[9] in physical dependence property. However, it is evident that this ratio of its analgesic dose (0.16 mg./kg.) in mice to the stabilizing dose (16 mg./kg.) in monkeys is nearly a hundred times more favorable than that of morphine (2 mg./kg. to 3 mg./kg.).



$X = Br, I$; a, $R = CH_3$; b, $R = CH_2CH_2C_6H_5$

Figure 1

EXPERIMENTAL

Microanalyses are by the Analytical Services Unit of this Institute, Harold McCann, director. Melting points were taken in a capillary. Infrared spectra (Perkin-Elmer, Model 21) are by H. K. Miller and Ann Wright, also of this institute.

4-Ethyl-1-p-methoxybenzyl-1-methyl-1,2,5,6-tetrahydropyridinium chloride (IIIa). To a stirred solution of 5.8 g. of Ia (X = I)[10] in 50 ml. of *N* sodium hydroxide was added in one lot 1 g. of sodium borohydride in 20 ml. of water. The temperature rose to 60° during 10 min. and was maintained at 50–60° for 3 hr. After addition of 4 g. of sodium chloride, the cooled mixture was extracted thrice with ether. Drying and evaporation of the ether left 3.1 g. of liquid IIa which, in 5 ml. of acetone, was treated (stirring) gradually with 4 g. of *p*-methoxybenzyl chloride[11] in a little acetone. The solution was stirred for 2 hr. and kept at −5° overnight to give, after filtration and washing with ether 5.6 g. (82%) of hygroscopic IIIa, m.p. 130° after drying

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(5) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959); J. H. Ager and E. L. May, *J. Org. Chem.*, **25**, 984 (1960).

(6) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

(7) E. L. May, *J. Org. Chem.*, **21**, 899 (1956).

(8) The test method used was that described in N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953).

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

(10) This compound, m.p. 105–110°, was prepared from 4-ethylpyridine and methyl iodide in acetone (reflux).

(11) T. F. Dankova, L. G. Evdokimova, I. I. Stepanow, and N. A. Preobrazhenski, *J. Gen. Chem.*, **18**, 1724 (1948); *Chem. Abstr.*, **43**, 2606 (1949).

for 3 days over phosphorus pentoxide *in vacuo;* $\lambda_{max}^{CHCl_3}$ 3.0, 4.01, 5.81, 5.92 μ.

Anal. Calcd. for $C_{16}H_{24}ClNO$: N, 4.97. Found: N, 4.84.

5-Ethyl-2'-hydroxy-2-methyl-6,7-benzomorphan (Va). To 15 g. of IIIa was added in one lot 100 ml. of *M* ethereal phenyllithium. Brisk refluxing ensued. After this subsided, the mixture was refluxed gently for 2 hr. and poured into ice water. The ethereal layer was extracted thrice with 10% hydrochloric acid.[12] The combined extracts were made alkaline with concd. ammonium hydroxide and shaken with 3 portions of ether. Evaporation of the dried ethereal extracts left an oil which was distilled to give 10 g. of crude IVa; b.p. 120–125°/0.3 mm. This and 40 ml. of 48% hydrobromic acid were kept at a bath temperature of 140° for 20 hr., made basic (ice–ammonium hydroxide) and extracted thrice with chloroform containing a little ethanol. The extracts were dried quickly and evaporated at the water pump. The residue crystallized from 15 ml. of hot acetone. After cooling overnight at −5° 4 g. (40% based on IIIa) of Va, m.p. 206–210° was obtained; cubes from methanol, m.p. 211–213°.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.54; H, 9.08; N, 5.98.

The *hydrochloride* crystallized from methanol-ether in colorless prisms, m.p. 256–258°; λ_{max}^{nujol} 3.2 μ.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.25; H, 8.28; N, 5.23. Found: C, 67.38; H, 8.50; N, 5.19.

4-Ethyl-1-(p-methoxybenzyl)-1-phenethyl-1,2,5,6-tetrahydropyridinium chloride (IIIb). 4-Ethylpyridine (10 g.), 20 g. of phenethyl bromide, and 30 ml. of ethanol were refluxed for 4 hr. and evaporated to dryness at the water pump. To 25 g. of residual oily Ib was added 4.2 g. of sodium hydroxide 60 ml. of water, and 100 ml. of methanol, then 4 g. of sodium borohydride (stirring). The temperature rose to 60° and was kept at 50–60° for 1.5 hr. The mixture was diluted with cold water and extracted thrice with ether. The combined extracts were washed with 25 ml. of cold water, dried over sodium sulfate, and evaporated to dryness leaving 18.5 g. of crude IIb whose *picrate* crystallized in yellow needles from methanol-acetone; m.p. 139–141°.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44; N, 12.61. Found: C, 56.95; H, 5.58; N, 12.64.

The remaining 18 g. of IIb, 25 ml. of acetone, and 14 g. of *p*-methoxybenzyl chloride were warmed briefly on the steam bath and left at 25° for 30 hr. Addition of 25 ml. of ether, thorough hand-stirring, and decantation left a white dough which was washed with another portion of ether. The residual IIIb was dried to constant weight at the water pump (bath temperature 50°) leaving 30 g. of nearly white, amorphous powder, $\lambda_{max}^{CHCl_3}$ 3.0, 4.1 μ.

Anal. Calcd. for $C_{23}H_{30}ClNO + 1/2\ H_2O$: C, 72.51; H, 8.20; N, 9.31. Found: C, 72.32; H, 8.23; N, 9.56.

5-Ethyl-2'-hydroxy-2-phenethyl-6,7-benzomorphan (Vb). To 15 g. of IIIb powder was added 140 ml. of *M* ethereal phenyllithium. After the initial, brisk ebullition the mixture was refluxed gently for 3 hr. and poured into ice water. The ether layer was shaken with 3 portions of 5% hydrochloric acid. The aqueous extracts containing precipitated oily hydrochloride of IVb was made alkaline with ammonium hydroxide and extracted with ether. Drying and evaporation of the extracts left 10.8 g. of crude IVb which, in 35 m. of 48% hydrobromic acid and 15 ml. of 30% hydrogen bromide in acetic acid, was kept at a bath temperature of 140–145° for 35 hr. (air condenser). The mixture was poured into ice and made alkaline with aqueous ammonia. Extraction with chloroform gave, after drying and evaporation, a residue which crystallized from acetone (−5°, overnight) in a yield of 3.7 g. (29% based on IIIb), m.p. 159–161°; cubes from methanol, m.p. 161–163°.

Anal. Calcd. for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.27; H, 8.68; N, 4.16.

The *hydrochloride,* crystallized from ethanol in cubes of m.p. 220–222°, λ_{max}^{Nujol} 2.9, 3.1 μ.

Anal. Calcd. for $C_{22}H_{28}ClNO.\ 1/2\ H_2O$: C, 72.01; H, 7.97; N, 3.82. Found: C, 72.06; H, 8.28; N, 4.00.

5-Ethyl-2'-methoxy-2-methyl-6,7-benzomorphan (VI) *hydrochloride.* Methanol (30 ml.), 2.9 g. of Va, and 45 ml. of 3% ethereal diazomethane were stirred to solution (1 hr.). After an additional 5 hr., 45 ml. more of the diazomethane solution was added, and the mixture was left at 25° for 3 days. Solvents were distilled *in vacuo* and the residue evaporatively distilled (160°, 0.3 mm.) giving 2.8 g. (91%) of VI. The hydrochloride salt crystallized from methanol-ether in prisms, m.p. 189–191°.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.16; H, 8.58; N, 4.97. Found: C, 68.14; H, 8.69; N, 4.96.

The *methiodide* of VI (from methanol) melted at 249–251°.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.71; H, 6.77; N, 3.62. Found: C, 52.54; H, 6.74; N, 3.66.

5-Ethyl-2'-methoxy-6,7-benzomorphan hydrochloride (VII). To 2.2 g. of cyanogen bromide in 15 ml. of chloroform was added during 1 hr. (stirring) 4.3 g. of VI in 30 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo.* The residue and 60 ml. of 6% hydrochloric acid were refluxed for 15 hr., cooled, made alkaline with ammonium hydroxide, and extracted with ether. Drying and evaporation of the extracts left 3.5 g. of oily VII whose hydrochloride crystallized from methanol-ether in needles, m.p. 199–201°.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.10; H, 8.30; N, 5.22.

5-Ethyl-2'-methoxy-2-phenethyl-6,7-benzomorphan hydrochloride. To a stirred mixture of 3.2 g. of VII, 5 ml. of ether, 3.5 g. of potassium carbonate, and 20 ml. of water was added, during 1 hr., 7.5 g. of phenylacetyl chloride in 15 ml. of ether. After 2 more hr. of stirring the ether layer was washed with dilute hydrochloric acid, then aqueous sodium bicarbonate. Drying and evaporation of the ether left 4.5 g. of crude phenylacetamide derivative of VII which in 50 ml. of ether was added gradually to 3 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was refluxed overnight and decomposed with 8 ml. of water and 8 ml. of *N* sodium hydroxide. Filtration and drying and evaporation of the filtrate left an oil which, with acetone–hydrogen chloride gave 3.1 g. (60%) based on VI) of hydrochloride, m.p. 234–236°; prisms from methanol, m.p. 244–246°.

Anal. Calcd. for $C_{23}H_{30}ClNO$: C, 74.27; H, 8.13; N, 3.77. Found: C, 74.42; H, 8.22; N, 3.75.

On refluxing a mixture of 1.5 g. of this hydrochloride, 20 ml. of 48% hydrobromic acid, and 20 ml. of acetic acid for 30 min. a 77% yield of Vb was obtained identical (infrared data, m.p., etc.) with that prepared from Ib as described above.

1-Ethyl-1,2-dihydro-7-methoxy-1-(2-dimethylaminoethyl)-naphthalene hydrochloride. The methiodide of VI (1.9 g.) and 30 ml. of 10% sodium hydroxide were refluxed for 2 hr. The oily methine was dried in ether and evaporatively distilled (180°, 0.5 mm.) giving 1.1 g. (86%). The hydrochloride crystallized from methanol-ether in flakes of m.p. 170–172°.

Anal. Calcd. for $C_{17}H_{26}ClNO$: C, 69.01; H, 8.86; N, 4.74. Found: C, 68.85; H, 8.65; N, 4.49.

1-Ethyl-1-(2-dimethylaminoethyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (IX) *hydrochloride.* The distillate directly above (0.9 g.), 50 mg. of platinum oxide, and 15 ml. of methanol absorbed one molar equivalent of hydrogen during 30 min. The filtered solution was evaporated to dryness leaving an oil whose hydrochloride crystallized from methanol-ether in long needles of m.p. 157–159°.

Anal. Calcd. for $C_{17}H_{28}ClNO$: C, 68.55; H, 9.47; N, 4.70. Found: C, 68.28; H, 9.38; N, 4.68.

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[12] From the ethereal layer, 1.1 g. of biphenyl, m.p. 65–68° and 0.6 g. of what appears to be 1,2-*bis*(*p*-methoxyphenyl)ethane, m.p. 124–126°; *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H. 7.49. Found: C, 79.15; H, 7.58. [*cf.* J. S. Buck and S. S. Jenkins, *J. Am. Chem. Soc.,* **51,** 2163 (1929)].

The *picrate* crystallized from methanol-acetone in yellow flakes, m.p. 136–138°.

Anal. Calcd. for $C_{23}H_{30}N_4O_8$: C, 56.32; H, 6.17; N, 11.42. Found: C, 56.38; H, 6.06; N, 11.16.

1-Ethyl-7-methoxynaphthalene (VIII). An intimate mixture of 0.5 g. of IX and 0.5 g. of 5% palladium charcoal was immersed in an oil bath preheated to 250°. The temperature of the bath was raised to 290° during 30 min. where it was maintained for another 30 min. The cooled mixture was extracted with ether and the extracts were washed with dilute hydrochloric acid. Drying and evaporation of the ether left a residue which was evaporatively distilled at 120° (bath temperature)/0.1 mm. giving 0.15 g. (42%) of crude VIII,[13] 0.1 g. of which was converted to the picrate (0.1 g. of picric acid, 5 ml. of methanol); yield 90 mg., orange needles from aqueous methanol, m.p. 85–87°.

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 54.94; H, 4.13; N, 10.12. Found: C, 54.69; H, 4.28; N, 10.65.

BETHESDA 14, MD.

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[13] The ultraviolet spectrum of this distillate in ethanol was consistent with the naphthalene structure.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Diuretics. VI. 1,2,4-Benzothiadiazine 1,1-Dioxides Substituted at 2,3,4- and 7-*N*-Sulfamoyl Positions

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Fluorobenzenes were chlorosulfonated to yield 2,4-bischlorosulfonylfluorobenzenes. These were converted to 2,4-bissulfamoylanilines and in turn to 4-alkyl-, aralkyl-, and aryl-1,2,4-benzothiadiazine 1,1-dioxides and their 3,4-dihydro analogues. Other benzothiadiazine 1,1-dioxide derivatives having alkyl and aralkyl groups in the 2, 3, and 7-*N*-sulfamoyl positions were prepared. Comparisons made of these compounds revealed interesting differences in their physical properties and their biological activities.

During the investigation of 1,2,4-benzothiadiazine 1,1-dioxides it became apparent that closely related 2- and 4-alkyl derivatives had marked differences in both their physical and biological properties.[1] Because of these interesting differences the study was extended to benzothiadiazine 1,1-dioxides and 3,4-dihydro analogues having alkyl, aralkyl, and aryl groups in 2,3,4 and 7-*N*-sulfamoyl positions. This paper describes the syntheses of the appropriate compounds and results of the comparisons of their physical properties and of their saluretic activities.

The usual methods of preparing 1,2,4-benzothiadiazines have been to chlorosulfonate anilines and thereby obtain 2,4-bischlorosulfonylanilines.[1] These are converted to sulfamoylanilines and then cyclized by an acylating agent. We found, and it has also been recently reported,[2,3] that fluorobenzenes are easily chlorosulfonated and the resulting 2,4-bischlorosulfonylfluorobenzenes are readily converted to 2,4-bissulfamoylanilines. The latter are very excellent precursors for 4- and some 2-and 3-substituted 1,2,4-benzothiadiazine 1,1,-dioxides. Chlorosulfonation of 1-chloro-3-fluorobenzene and 1-fluoro-3-methylbenzene yielded 5-chloro-2,4-bis(chlorosulfonyl)fluorobenzene and 2,4-bis(chlorosulfonyl)-5-methylfluorobenzene, respectively. The sulfonylchlorides were treated with liquid ammonia and also with dilute aqueous ammonia to yield sulfonamides (I). Both alkyl- and arylamines reacted with the 2,4-bissulfamoylfluorobenzenes (I) by displacing the fluorine with formation of *N*-alkyl- and *N*-arylanilines (II). Displacement of the fluorine with the more basic methyl- and ethylamines (*pK* 10.62 and 10.63) occurred rapidly at room temperature while reactions with aniline (*pK* 4.7) required a higher temperature for reasonably rapid completion. Dilute aqueous ammonia solutions (*pK* 9.21) of I were concentrated by boiling without conversion to the 2,4-bis-sulfamoylanilines (II. R = H). We assume that, at least in the case with ammonia, the displacement is not entirely *pK* dependent.

N-Alkylsulfamoyl and *N*-benzylsulfamoylanilines were prepared by treating 5-chloro-2,4-bischlorosulfonylaniline with appropriate alkylamines or with benzylamine. A method described by Close and co-workers[4] was used to introduce a substituent only on the nitrogen of the sulfamoyl group *ortho* to the amino group. The products in the first case were 2,4-bis- *N*-alkylsulfamoyl-5-chloroanilines (VII. R and R_1 = alkyl), and 2,4-bis-*N*-benzylsulfamoyl-5-chloroanilines (VII. R and R_1 = benzyl). In the second case, 6-chloro-3,4-dihydro-3-keto-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide[4] was benzylated with benzyl bromide and sodium in *N*,*N*-dimethylformamide solution to yield 2-benzyl-6-chloro-3,4-dihydro-3-keto-7-

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[1] F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

[2] B. G. Boggiano, S. Condon, M. T. Davies, G. B. Jackman, B. G. Overell, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **12**, 419 (1960).

[3] G. B. Jackman, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **12**, 648 (1960).

[4] W. L. Close, L. R. Swett, L. F. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).