thesis, to Mrs. Nancy Engstrom and Mr. Urs Stoeckli for instrumental determinations, and to Mr. William Bonkoski for the microanalyses.

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Neuroleptic Agents of the Benzocycloheptapyridoisoquinoline Series. 1. Syntheses and Stereochemical and Structural Requirements for Activity of Butaclamol and Related Compounds†

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The syntheses and the structural and stereochemical requirements for antagonism of (+)-amphetamine-induced stereotypy are described for a series of benzocycloheptapyridoisoquinoline derivatives. One of these compounds, (±)-(4a,13b-*trans*)[3(OH),13b(H)-*trans*]-3-*tert*-butyl-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol hydrochloride (butaclamol hydrochloride, USAN), is currently being studied in man. The relationship between structure and antiamphetamine activity in this class of compounds is discussed.

Recently, we reported[1] syntheses of the 4a,13b-cis and the 4a,13b-trans isomers of the 1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline **1**, the trans isomer exhibiting actions characteristic of antianxiety drugs in laboratory animals.[2] One of the synthetic paths utilized in that study[1] involved the removal of oxygen from the isomeric amino ketones **2** and **3**. The present report describes the synthesis and stereochemistry of a series of tertiary carbinols obtained *via* transformations of the amino ketones **2** and **3**. One of these tertiary carbinols, butaclamol hydrochloride (**4**, USAN),‡ is a neuroleptic agent currently undergoing clinical evaluation.[3] Some pharmacological properties of **4** and related compounds will be described in this report. A detailed description of the psychopharmacological profile of butaclamol hydrochloride has recently been submitted for publication by Voith and Herr.[4]

Chemistry. The compounds prepared (see Table I) were obtained, in moderate yields (25-40% after purification), by the reaction of the *cis*- or *trans*-amino ketones (**2**, **3**) with a Grignard reagent or with a hydrocarbon lithium (see Experimental Section). For those compounds derived from the 4a,13b-*trans*-amino ketone the configurations at the tertiary carbinol center were assigned on the following basis. Inspection of a molecular model of *trans*-amino ketone **2** shows that, in its most stable conformation (see Scheme I), ring A is situated on the α face of the plane formed by rings C, D, and E and is oriented to it by an

1

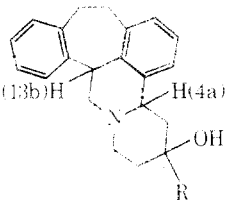2 (4a,13b)-trans
3 (4a,13b)-cis

4
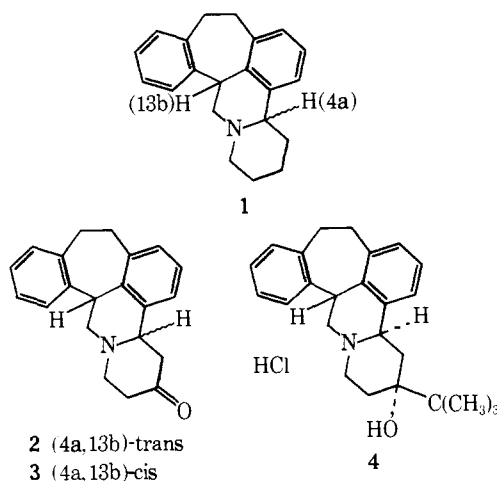
angle of about 120°. Nucleophilic attack on the carbonyl group from the α face of the molecule (axial attack) is unfavorable because of the steric effect of ring A. In contrast, equatorial attack from the β face of the molecule is not subject to the influence of ring A. Experimentally, the reaction of the *trans*-amino ketone **2** with ethylmagnesium bromide afforded **6** which is consequently assigned the 3(OH),13b(H)-trans relative configuration since it is assumed to be formed by equatorial approach by the anionic species.

Hennion and O'Shea[5] have demonstrated that the small, linear acetylide anion reacts with 4-*tert*-butylcyclohexanone by axial attack to afford a product in which the *tert*-butyl and ethynyl groups bear a cis relationship. We

Table I. Chemical Data and Effects on (+)-Amphetamine-Induced Stereotypy for 3-Substituted Benzo[6,7]cyclohepta[1,2,3-de]pyrido[2,1-a]isoquinolin-3-ols

No.	R	4a,13b rel config	3(OH),- 13b(H) rel config	Mp, °C	Crystn solvent[a]	Formula[b] (analyses)	Antagonism of ASB,[c] MED, mg/kg ip
5	Methyl	Trans	Unknown	254–256	A	C$_{22}$H$_{25}$NO·HCl (Cl, N)	>20[d]
6	Ethyl	Trans	Trans	262–265	A	C$_{23}$H$_{27}$NO·HCl (Cl, N)	10
7	Ethyl	Cis	Trans	245–249	A	C$_{23}$H$_{27}$NO·HCl (Cl, N)	e
8	Ethyl	Trans	Cis	212–214	B, C	C$_{23}$H$_{27}$NO·HCl (Cl, N)	e
9	Ethyl	Cis	Cis	140–142	A, E	C$_{23}$H$_{27}$NO (C, H, N)	Inactive[f]
10	Ethynyl	Trans	Cis	280–282	B, C	C$_{22}$H$_{23}$NO·HCl (Cl, N)	Inactive
11	Ethynyl	Cis	Cis	176–178	D, E	C$_{22}$H$_{23}$NO (C, H, N)	Inactive
12	n-Propyl	Trans	Trans	290–291	A	C$_{24}$H$_{29}$NO·HCl (C, H, Cl, N)	15
13	Cyclopropyl	Trans	Trans	260–262	A	C$_{24}$H$_{27}$NO·HCl (C, H, Cl, N)	1.25
14	2-Propyl	Trans	Trans	287–289	A	C$_{24}$H$_{29}$NO·HCl (Cl, N)	1.25
15	Allyl	Trans	Unknown	280–282	A	C$_{24}$H$_{27}$NO·HCl (Cl, N)	>20
16	n-Butyl	Trans	Trans	287–289	A, C	C$_{25}$H$_{30}$NO·HCl (Cl, N)	10
4	tert-Butyl	Trans	Trans	282–284	A	C$_{25}$H$_{31}$NO·HCl (C, H, Cl, N)	0.62
17	tert-Butyl[g]	Cis	Trans	238–239	A	C$_{25}$H$_{31}$NO·HCl (C, H, Cl, N)	Inactive
18	n-Hexyl	Trans	Trans	285–287	A	C$_{27}$H$_{35}$NO·HCl (C, H, Cl, N)	5.0
19	Cyclohexyl	Trans	Trans	312–314	B	C$_{27}$H$_{33}$NO·HCl (Cl, N)	1.25
20	Phenyl	Trans	Trans	290–292	A	C$_{27}$H$_{27}$NO·HCl (C, H, Cl, N)	2.5
21	Chlorprom-azine						7.5
22	Fluphen-azine						0.5
23	Droperidol						0.62

[a]A = acetone; B = methanol; C = ether; D = benzene; E = hexane. [b]Compounds were analyzed for the elements shown in brackets. All results were within ±0.4% of the calculated values. [c]ASB = amphetamine-induced stereotyped behavior. [d]>20 indicates that a partial antagonism was attained at the 20 mg/kg dose; however, to fulfill the criterion of antagonism, larger doses are needed. See Pharmacology section for details. [e]The antiamphetamine efficacy of these compounds was not evaluated by the amphetamine-induced stereotyped behavior but by another experimental model. For details see text. [f]"Inactive" indicates that at a dose of 20 mg/kg, the behavior of the "amphetamine + compound" treated rats did not differ from that of "amphetamine + vehicle" treated control animals. [g]This compound was prepared by Dr. K. Pelz of our laboratories.

Scheme I
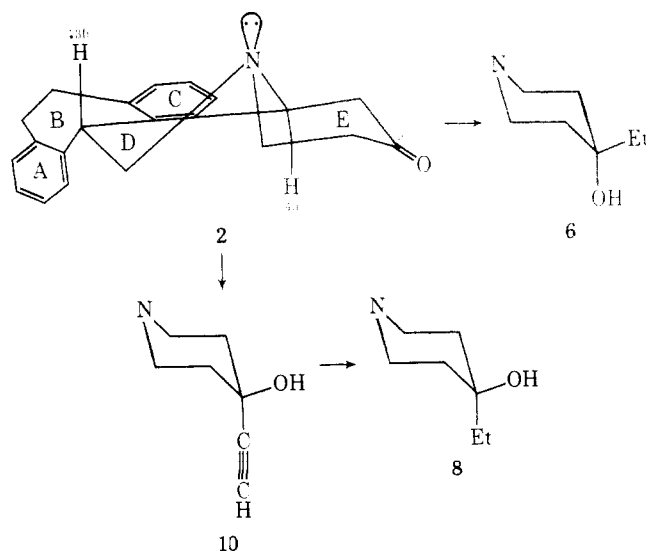
have similarly reacted the trans-amino ketone 2 with sodium acetylide to afford 10 in 88% yield and, after reduction

of the triple bond, have obtained the ethylcarbinol 8. This isomer is assigned the 3(OH),13b(H)-cis relative configuration.

By analogy, all compounds in Table I which are prepared by the reaction of the trans-amino ketone 2 with an anionic species bulkier than the ethyl group are assigned a 3(OH),13b(H)-trans relative configuration. No configurational assignments have been made for the methyl and allyl tertiary carbinols 5 and 15.

A similar interpretation of the effect of ring A on the stereochemical course of the reactions of anionic species with the cis-amino ketone 3 leads to the assignment of a 3(OH),13b(H)-trans relative configuration for the ethyl- and tert-butylcarbinols 7 and 17 and a 3(OH),13b(H)-cis relative configuration for the ethyl- and ethynylcarbinols 9 and 11.

The assigned relative configurations at position 4a and 13b[1] and at the 3 position in compound 4 (butaclamol hydrochloride) have recently been confirmed by an X-ray crystallographic study.[6]

Pharmacology. Introduction. It has been shown over the past several years that compounds possessing diverse chemical structures share a number of pharmacological effects and exert antipsychotic activity in the clinic.

Among the various pharmacological actions, the antagonism of the amphetamine-induced stereotypy in rats is one of the most selective and sensitive tests for neuroleptics.

The amphetamine stereotyped behavior may be regarded as a model psychosis.[7,8] This is based upon the observations that (1) amphetamine induces stereotyped activities in serveral mammalian species and psychosis in man;[7-9] (2) that the amphetamine-induced psychosis shows close clinical similarity to acute paranoid schizophrenia;[10-12] (3) that neuroleptic drugs antagonize the amphetamine stereotyped behavior with high specificity;[8,13-18] and (4) that there is a high correlation between the antiamphetamine effect of the neuroleptic drugs in rats and their antipsychotic efficacy in humans.[7,8,14,19] Studies carried out over the past several years have shown that the action of amphetamine in eliciting the stereotypy is indirect[20] and probably mediated through dopamine.[7,8,20-23]

Recently, it has been suggested[24,25] that the dopaminergic mechanisms are more important than the noradrenergic ones in eliciting amphetamine psychoses in man. It has been further shown[26] that in doses which specifically blocked dopamine, haloperidol effectively antagonized the amphetamine-induced psychosis. Both findings support the assumption that amphetamine stereotyped behavior in rats is a valid model for human psychosis, and, therefore, this model has been used to evaluate. the novel compounds described in this report.

Methods. The experimental procedure used to evaluate the antagonism of amphetamine-induced stereotyped behavior in rats was based on the methods of Randrup, *et al.*,[13] Herman,[15] and Janssen, *et al.*[27] Male Sprague–Dawley rats (160–200 g) were placed in groups of four, in metal cages (43 × 25 × 23 cm) with wire grid bottoms, and (+)-amphetamine sulfate was injected ip at a dose of 10 mg/kg, followed 15 min later by an ip injection of graded doses of the compounds, or of the vehicle. The highest dose evaluated was 20 mg/kg.

The stereotyped behavior has a rapid onset of action, reaches a peak by the end of the first hour, and starts to subside toward the end of the third hour. Observations were made every 15 min starting after the injection of amphetamine, for a total of 4 hr, and the behavior of the rats was classified into one of the following categories: (1) normal—the rats divided their time between occasional exploration, sniffing, grooming, and sleeping; (2) excited—the rats sniffed almost constantly at the wire netting of the cage, mostly at the walls and ceiling; sniffing of the floor occurred only transiently; the rats moved around in the cage and kept their heads elevated; (3) stereotyped—the rats kept their nose on the floor without any interruption; they sat in a crouched position and continuously licked or bit the wires of their cage, moving at regular intervals from one wire to another; normal activities and forward locomotion were absent while backward locomotion occurred occasionally.

The results are expressed as the minimal effective dose (MED) in milligrams per kilogram. The MED was arbitrarily defined as the dose which antagonized all the behavioral effects of amphetamine during the entire 4-hr experimental period. Chlorpromazine, the prototype of neuroleptic drugs, fluphenazine, one of the most potent phenothiazine derivatives, and, droperidol, a potent butyrophenone, were used as reference standards. All doses were calculated as the free base.

Results and Discussion

The activity of 17 benzocycloheptapyridoisoquinoline

derivatives against amphetamine-induced stereotyped behavior in rats is summarized in Table I. It is evident that the antiamphetamine efficacy, which is indicative of neuroleptic activity in man, is critically dependent on the relative configurations at positions 3, 4a, and 13b. Thus, of the four possible racemic pairs of the ethylcarbinols 6-9, only 6, having a 4a,13b-trans and a 3(OH),13b(H)-trans configuration, shows antiamphetamine activity. Similarly, 4 (butaclamol hydrochloride), a compound with the required 4a,13b-trans and 3(OH),13b(H)-trans configurations, is highly active, while the corresponding 4a,13b-cis isomer 17 is inactive.

Two of the ethylcarbinols (7, 8) were not tested in the amphetamine stereotypy model. Instead, their antiamphetamine efficacy was evaluated in aggregated mice according to the method of Proctor, *et al.*[28] In doses up to 10 mg/kg ip, neither compound 7 nor 8 protected aggregated mice against the lethal effect of amphetamine. Compound 9 was likewise inactive in this model at 10 mg/kg. In contrast, compound 6 protected 100% of the mice against the lethal effect of amphetamine at the 10 mg/kg dose level. While 6 abolished the amphetamine-induced stereotyped behavior at 10 mg/kg, 9 was inactive in doses up to 20 mg/kg. Thus, it can be assumed that 7 and 8 would be inactive also against the amphetamine-induced abnormal behavior in rats.

The ethyl (6), *n*-propyl (12), *n*-butyl (16), and *n*-hexyl (18) substituted carbinols possessing unbranched hydrocarbon chains exert an activity which is comparable to that of chlorpromazine (21). The methylcarbinol 5 shows only weak antiamphetamine activity at 20 mg/kg. It is not apparent whether the weak activity of 5 is due to the size of the alkyl group or to an unfavorable 3(OH),13b(H)-cis relative configuration.

Compounds of exceptionally high activity, in the range of fluphenazine (22) and droperidol (23), are obtained when the side chain is branched or incorporated into an alicyclic ring. Thus, the cyclopropyl (13), 2-propyl (14), and cyclohexyl (19) analogs were active at 1.25 mg/kg, and the *tert*-butyl analog 4 was active at 0.62 mg/kg.

The phenyl derivative 20 was active at 2.5 mg/kg while the ethynyl intermediates 10 and 11, both having the "wrong" 3(OH),13b(H)-cis relative configuration, were devoid of activity. The allyl derivative 15 showed only weak activity at the screening dose of 20 mg/kg. As pointed out above, the stereochemistry at position 3 is unknown in this compound so that a distinction cannot be made between constitutional and configurational factors which could be responsible for the weak activity of this compound.

In conclusion, this study has identified a new class of compounds possessing high antiamphetamine activity in animals. One of these compounds, butaclamol hydrochloride (4), has been shown to be an effective neuroleptic agent in man.[3] Apart from the novel structure of 4 which distinguishes it from the neuroleptic agents currently in clinical use,[29] the present compounds are rendered unique by their very limited conformational flexibility and by the specific configurational requirements at positions 3, 4a, and 13b, which are mandatory for activity. A detailed analysis of the stereochemical features of compounds of this class, and the potential significance of these features with regard to the topography of the central dopamine receptor, will be the subject of a separate report.[30]

Experimental Section

H, and N analyses were done with a Perkin-Elmer Model 240 C, H, N analyzer.

(±)-(4a,13b-*trans*)[3(OH),|13b(H)-*trans*]-3-Ethyl-2,3,4,4a,8,9,-13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol Hydrochloride (6). A solution of 2^1 (10.0 g, 0.033 mol) in benzene (100 ml) was added to an eth-ylmagnesium bromide solution prepared from ethyl bromide (10 ml) and Mg (5 g) in ether (100 ml). The mixture was stirred at 22° for 1 hr and then water was added. The ether phase afforded an oil (13 g) which was dissolved in ether and treated with anhy-drous HCl. The crude HCl salt was crystallized from acetone to afford the product (3.5 g, 28%), mp 262–265° (Me₂CO).

A similar reaction of 2 with the Grignard reagent prepared from the appropriate hydrocarbon bromide afforded compounds 12, 13, 15, 16, 18, and 20. Compound 19 was prepared from 2 and cyclo-hexylmagnesium chloride, and 7 was obtained from the reaction of 3 and ethylmagnesium iodide (see Table I).

(±)-(4a,13b-*trans*)[3(OH),13b(H)-*trans*]-3-*tert*-Butyl-2,3,4,-4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]-pyrido[2,1-*a*]isoquinolin-3-ol Hydrochloride (4). To a solu-tion of *tert*-butyllithium in pentane (0.32 mol; 175 ml of a 1.8 *M* solution) at 0° was added a solution of 2 (25 g, 0.08 mol) in ben-zene (400 ml) during 30 min. The temperature was kept at 5–10° during the addition and for 60 min thereafter. The reaction mix-ture was treated with 10% aqueous NH₄Cl solutions (150 ml) and the organic phase was treated in the conventional manner to af-ford an oil (33 g). It was dissolved in MeOH and treated with an-hydrous HCl. The crude HCl salt was crystallized from acetone to afford the product (9.5 g, 30.5%), mp 282–284°.

A similar reaction of 2 with methyllithium afforded 5, and with 2-propyllithium, 14 was obtained. Compound 17 was prepared by the reaction of 3^1 with *tert*-butyllithium (see Table I).

(±)-(4a,13b-*trans*)[3(OH),13b(H)-*cis*]-3-Ethynyl-2,3,4,4a,8,-9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido-[2,1-*a*]isoquinolin-3-ol Hydrochloride (10. Sodium acetylide was prepared by bubbling acetylene into a solution of NaNH₂ prepared from Na (2.5 g) and liquid NH₃ (200 ml) in the presence of ferric nitrate catalyst. To this mixture was added 2 (3.0 g, 0.01 mol) in THF (30 ml). The reaction mixture was kept cold with CO₂-Me₂CO for 3 hr, then NH₄Cl (5.0 g) was added, and the NH₃ was allowed to evaporate. H₂O was added and the mixture was extracted with EtOAc. A conventional treatment of the EtOAc extract afforded the free base of the product in 88% yield: mp 165–166° (hexane). The HCl salt had mp 280–282° (MeOH-Et₂O).

Compound 11 was prepared in the same manner as described above, in 76% yield, except that 3 was used instead of 2 (see Table I).

(±)-(4a,13b-*trans*)[3(OH),13b(H)-*cis*]-3-Ethyl-2,3,4,4a,8,9,-13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido-[2,1-*a*]isoquinolin-3-ol Hydrochloride (8). Compound 10·free base (2.1 g, 0.006 mol) in EtOH (25 ml) was hydrogenated at atmospheric pressure and at 22° in the presence of PtO₂ (40 mg). A conventional work-up procedure afforded an oil (1.7 g). It was dissolved in Et₂O and treated with anhydrous HCl to afford the product (1.1 g, 47%), mp 212–214° (MeOH-Et₂O).

A similar reduction of 11 gave compound 9 in 52% yield (see Table I).

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