Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.5; H, 6.7; N, 7.2; O, 24.6; alkoxyl as OCH_3, 0.0. Found: C, 61.0; H, 6.8; N, 7.1; O, 24.8; alkoxyl as OCH_3, 0.0.

The material was assayed by the colorimetric ninhydrin method of Troll and Cannan[9] using phenylalanine as a standard. If one assumes that the color yield of *p*-(hydroxymethyl)phenylalanine is the same as that of phenylalanine, the product is calculated to be 98% pure.

The compound possesses the following spectral characteristics in water solution: λ_{min} 280, 239 mμ (ε 20, 141); λ_{max} 270 (sh), 265 (sh), 262, 257 (sh), 252, below 239 mμ (ε 160, 235, 292, 263, 217, end absorption). Its ultraviolet absorption spectrum is distinct from that of DL-phenylalanine and DL-*p*-methylphenylalanine (Figure 1). Its infrared spectrum[10] (Nujol mull) showed bands at 860, 1015, 1160, 1210, 1310, 1340, 1410 cm.$^{-1}$ in the 800–1500-cm.$^{-1}$ region. The peak at 1015 cm.$^{-1}$ is not found in spectra of DL-phenylalanine or DL-*p*-methylphenylalanine.

Paper chromatography of the compound in the system[11] 1-butanol–acetic acid–water, 200:30:75 (Whatman 3 MM paper ascending for 15 hr.), revealed a single ninhydrin staining spot (R_f 0.34). The migration of the compound in this system differs markedly from that of authentic DL-phenylalanine (R_f 0.52) or DL-*p*-methylphenylalanine (R_f 0.64).

(9) W. Troll and R. K. Cannan, *J. Biol. Chem.*, **200**, 803 (1953).

(10) These measurements were performed by Dr. C. H. Winestock.

(11) "Specifications and Criteria for Biochemical Compounds," Publication 719, National Academy of Sciences, National Research Council, Washington, D. C., 1960, p. AAi.

Coupling Reactions in the Synthesis of Amitriptyline

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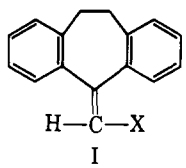
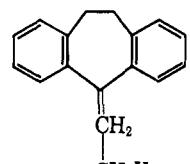
Received February 24, 1965

The readily available bromo compounds I and II (X = Br) provide new and direct routes to amitriptyline systems in fair to moderate yields by direct coupling of their Grignard derivatives with β-dimethylaminoethyl chloride and isobutoxymethyldimethylamine, respectively. Hydrocarbon dimers are by-products in each case.



I



II

Experimental

5-Bromomethylene-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I, X = Br).—A solution of 1.85 g. of 5-methylene-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (I, X = H)[1] in 15 ml. of chloroform was brominated by dropwise addition of 1.45 g. of bromine dissolved in 9 ml. of $CHCl_3$. Bromine absorption was instantaneous, accompanied by copious evolution of HBr. The reaction mixture was evaporated to dryness and crystallized from petroleum ether (b.p. 30–60°); yield 2.5 g., m.p. 70–72°. A sample crystallized for analysis melted at 73–75°.

Anal. Calcd. for $C_{16}H_{13}Br$: C, 67.37; H, 4.56; Br, 28.08. Found: C, 66.98; H, 4.46; Br, 28.17.

5-(3-Dimethylaminopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene Hydrochloride (Amitriptyline; I, X = $CH_2CH_2N(CH_3)_2 \cdot HCl$). A. From I, X = Br.—The corresponding Grignard reagent was prepared by adding slowly under nitrogen a solution of 2.00 g. of the 5-bromomethylene compound I (X = Br) in 10 ml. of tetrahydrofuran to a stirred mixture of 170 mg. of magnesium turnings and 2 ml. of tetrahydrofuran. The reaction was started by initially adding a trace of methyl iodide. When addition of I (X = Br) was complete, the dark brown solution was refluxed for 90 min. It was then cooled to room temperature and a solution of 760 mg. of β-dimethylaminoethyl chloride[2] was added. The stirred mixture was refluxed for 2 hr., kept at room temperature overnight, and worked up by cooling to 10° and adding 20 ml. of 10% aqueous NH_4Cl and 10 ml. of 2.5 *N* HCl. Following ether extraction the acidic layer was made basic with 2.5 *N* NaOH and extracted with ether. From the latter extract 230 mg. of basic material was obtained which on treatment with HCl in ether and crystallization from ether gave 170 mg. (20% based on recovered I, X = H; see below) of amitriptyline (I, X = $CH_2CH_2N(CH_3)_2 \cdot HCl$), m.p. 175–190°, raised to 192–194° on one recrystallization from ether–2-propanol. On admixture with an authentic sample of m.p. 192–194°, there was no melting point depression and the respective infrared spectra were identical.

The neutral ether extract (1.150 g.) on alumina chromatography gave 810 mg. (56%) of reusable 5-methylene compound I (X = H), m.p. 60–63°, and 25 mg. of the dimer I [X = ( )$_2$] crystallized from acetone; m.p. 270–271°, $\lambda_{max}^{dioxane}$ 318 mμ (ε 33,000).

Anal. Calcd. for $C_{32}H_{26}$: C, 93.61; H, 6.38; mol. wt., 410. Found: C, 93.27; H, 6.33; mol. wt., 398.[3]

B. From II, X = Br.—A "cyclic reactor" based on a design by Greenlee[4] was employed in the Grignard reaction to minimize coupling. This reactor consisted, in ascending order, of a 100-ml. three-neck reservoir flask (two necks stoppered) of refluxing ether, a side-arm column containing magnesium turnings immersed in ether, a condenser, and a dropping funnel with a nitrogen inlet. The magnesium in the reactor column was amalgamated by standing overnight under a saturated ether solution of $HgBr_2$. After draining this solution, the reactor column was refluxed with ether for 1.5 hr.; and finally, the magnesium was further activated with 0.2 ml. of methyl iodide in 1 ml. of ether followed by refluxing in ether for 1.5 hr. In these and all subsequent steps the ether level in the reactor was maintained just above the surface of the magnesium, and the system was kept under dry nitrogen. The reservoir flask was charged with 15 ml. of dry ether and refluxing was begun. The dropwise return rate (from the reactor column to the reservoir flask) was adjusted such that the ether level in the reactor remained constant. One gram (3.34 mmoles) of 5-(β-bromoethylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene (II, X = Br)[5] dissolved in 30 ml. of dry ether was added to the reactor column at a steady rate of 1 drop/30 sec. (ratio of reflux-drop rate to addition-drop rate was 30:1). Addition was complete in 3.5 hr., after which time the reactor column was refluxed for an additional 30 min. The reaction mixture was cooled to 25°, the reactor column assembly on the reservoir flask was replaced by a stirrer, and a reflux condenser (with nitrogen inlet) and addition funnel were added to the previously stoppered necks of the reservoir flask. A solution of 0.433 g. (3.30 mmoles) of isobutoxymethyldimethylamine[6] in 10 ml. of dry ether was added dropwise with stirring to the Grignard solution over a period of 5 min. The resulting mixture was refluxed for 0.5 hr., kept overnight at room temperature, and refluxed an additional hour. The reaction mixture was chilled in an ice bath and treated with 20 ml. of saturated NH_4Cl solution. The aqueous layer was extracted with ether, and the ether extract was washed successively with 10 ml. of 2.5 *N* HCl and 15 ml. of water. The aqueous phase was made alkaline with concentrated NH_4OH and extracted with ether. The basic ether extract was washed with 15 ml. of saturated salt solution, dried ($MgSO_4$), and evapo-

(1) W. Treibs and H. J. Klinkhammer, *Ber.*, **83**, 367 (1950).

(2) Freshly prepared from the corresponding hydrochloride; see E. Knorr, *ibid.*, **37**, 3507 (1904); R. B. Burtner, *J. Am. Chem. Soc.*, **71**, 2578 (1949).

(3) The molecular weights were determined by means of a Mechrolab vapor pressure osmometer.

(4) K. W. Greenlee, D. C. Rowlands, C. E. Boord, Abstracts, 117th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1950, p. 8L. We are grateful to Dr. Greenlee for communicating to us details of this method.

(5) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Med. Chem.*, **7**, 392 (1964).

(6) R. Robinson, *J. Chem. Soc.*, 532 (1923).

rated to dryness *in vacuo* to yield 540 mg. (58.3% yield)[7] of oily free amine. The neutral ether extract was washed with 15 ml. of saturated salt solution, dried ($MgSO_4$), and taken to dryness *in vacuo* to yield 280 mg. of a neutral yellow oil.

The free amine in 10 ml. of ether was treated with 4 ml. of ether saturated with HCl, and the mixture was taken to dryness. The gummy residue was dissolved in ethanol, treated with charcoal, and filtered through Celite. The filtrate, when boiled down to a small volume, diluted with ether to the point of cloudiness, and scratched, yielded 460 mg. (43.8%) of amitriptyline (II, X = $CH_2N(CH_3)_2 \cdot HCl$), m.p. 180–185°.

The 280 mg. of neutral oil on chromatography over 25 g. of basic alumina yielded on elution with hexane 127.4 mg. of crystalline coupled hydrocarbon II [X = (½], m.p. 121–124°, $\lambda_{max}^{methanol}$ 207 mμ (ε 86,500) and 239 (23,400).

Anal. Calcd. for $C_{31}H_{30}$: C, 93.11; H, 6.89; mol. wt., 410. Found: C, 92.81; H, 6.75; mol. wt., 443.[5]

(7) The yield of Grignard reagent estimated by titration was *ca.* 65–70%. Therefore, reaction with isobutoxymethylenedimethylamine must have occurred in good (80–90%) yield.

Book Review

Psychopharmacological Agents. Volume I. Edited by MAXWELL GORDON (Volume IV in the series, Medicinal Chemistry, G. de Stevens, Ed.). Academic Press Inc., New York, N. Y. 1964. xvi + 678 pp. 23.5 × 16.5 cm. $23.50.

In the last decade the pace of expansion of medicinal chemistry has been stepped up so rapidly that a reasonably thorough coverage of any one of its many areas is no longer feasible except in specialized monographs. The present volume is the first of two devoted to the drugs which influence the state of the mind, and which have brought about revolutionary changes in the treatment of mental diseases.

The book has been written by and for medicinal chemists and pharmacologists who are interested in psychopharmacological agents. Each chapter starts with the background of the discovery of the type of drug under discussion. In some cases a follow-up on ancient folklore has been operative, in others the observation of certain types of psychopharmacological side effects of established drugs with unrelated activities. More often, however, there has been a lack of causative mind processes which opened a new field to investigation. These stories are being told by the very men to whom these discoveries are credited, and thus they form an authentic documentation of those early researches. An excellent account of the chemical derivations of the drugs, their syntheses, steric considerations, and structure–activity relationships is presented in each chapter. These sections are followed by carefully compiled and restrained sections on the general and psychopharmacology of each major drug, and often, many of its congeners. The fine shades of symptomatic differences in the animal experiments are considered together with basic actions which might explain the observed symptoms. Side effects are listed detachedly, and these particular sections attest to the highmindedness of the many investigators in an extremely competitive industry.

The *in vivo* fate of the major drugs has given much insight into the mechanism of action of the various agents, and in some cases, has led to the discovery of activation by metabolic alteration. Some of these studies are among the best contributions of biochemistry to modern medicinal science.

Although, or perhaps because, the book represents a close-to-ideal cooperative effort of chemists and experimental biologists, sections on the clinical applications of the drugs described have been held at a minimum. They survey the clinical utility, advantages, and disadvantages of the major drugs for mental diseases, but do not give the psychiatrist or the general practitioner quite enough information for the use of these drugs on his patients. However, excellent lists of clinical references make up for this intended deficiency.

The first volume presents all types of psychopharmacological agents except the phenothiazines which will fill Volume II as a monograph on this topic. Among the subjects in Volume I are the Rauwolfia drugs, the dibenzazepines, meprobamate, chlorodiazepoxide and related compounds, the lead compounds and congeners of the methylphenidate and pipradol group, piperazine derivatives, thiaxanthenes, benzimidazoles and related systems, and all types of inhibitors of monoamine oxidases. Chapters on benactyzine and on psychotomimetic compounds make strange bed-fellows in this sound assembly, but seem to have been included as fringe benefits for the reader. The list of authors reads like a Who's Who in psychopharmacological science; the editor has done an unusually conscientious job to unify the thirteen chapters into a continuous and homogeneous whole. A complete author index and a subject index add to the utility of the book.

This review was written on the sand of Waikiki Beach on an April Sunday, while the reviewer tried to relax from a full week's laboratory work on the biochemistry of some of the very drugs described in this volume. It must be reported that reading about these drugs, without sampling some of them, did not facilitate mental concentration in the presence of the many vital and absorbing distractions in the natural environment.

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