dimethyldibenzylamine (I) and the corresponding N-amino compound (II) were prepared by the route

$$C_6H_5CH(CH_3)NH_2 + C_6H_5COCH_3 \longrightarrow$$
$$[\alpha]^{25}D\ -40.03^\circ$$
$$C_6H_5CH(CH_3)N{=}C(CH_3)C_6H_5$$
$$III,\ [\alpha]^{25}D\ -97.56^\circ$$

$$III \xrightarrow[H_2]{Pd/C} [C_6H_5CH(CH_3)]_2NH \xleftarrow{HONO}$$
$$IV,\ [\alpha]^{25}D\ -196.3^\circ$$
$$[C_6H_5CH(CH_3)]_2NNO$$
$$I,\ [\alpha]^{20}D\ -259.1^\circ$$

$$I \xrightarrow[EtOH]{Na} [C_6H_5CH(CH_3)]_2N{-}NH_2$$
$$II,\ [\alpha]^{20}D\ -115.8^\circ$$

Catalytic reduction of (III), b.p. 106° (0.2 mm.) (*Anal.* Found: C, 86.12; H, 7.71; N, 6.52) gave 88% of one optical antipode of IV, b.p. 103–105° (0.3 mm.) (*Anal.* Found: C, 85.44; H, 8.36; N, 6.44). Reduction predominantly from one side can be explained by molecular models which show that the benzylidene phenyl cannot rotate freely and is twisted out of the C–C=N plane. This out of plane deformation is supported by spectral evidence. Both the nitrosation of IV to I, m.p. 56–57° (*Anal.* Found: C, 75.55; H, 7.33; N, 10.95) and the reduction of I to II, b.p. 120° (0.1 mm.) (*Anal.* Found: C, 80.14; H, 8.21; N, 11.44) proceeded without racemization. The optical purity of I and II was determined by reconversion to IV, the optical purity of which had been determined previously by catalytic debenzylation to the known α-methylbenzylamine.

Optically pure 2,3-diphenylbutane (V) $[\alpha]^{20}D$ + 85.5° (ethanol), was prepared by nitration and subsequent catalytic reduction of DL-2,3-diphenylbutane to give DL-*p,p'*-diamino-2,3-diphenylbutane (VI) m.p. 84–85.5° (*Anal.* Found: C, 80.08; H, 8.27; N, 11.33) which was resolved using D-tartaric acid. Subsequent deamination gave V.

Hydrosulfite reduction of I proceeded with 90% evolution of nitrogen to give 21.2% *meso* and 43% liquid 2,3-diphenylbutane having an $[\alpha]^{20}D$ of −45.5°. The mercuric oxide oxidation of II proceeded with even less retention of configuration giving 31.2% *meso* and 45% liquid hydrocarbon having an $[\alpha]^{20}D$ −36.4°, the theoretical amount of nitrogen being evolved. The 2,3-diphenylbutanes were the only products identified—no styrene or polystyrene could be isolated.

The stereochemical results for the case reported here suggest that the elimination of nitrogen and formation of coupled product does not proceed by a completely concerted process. In the case of the substituted piperidines[1,2] formation of cyclic product was interpreted as arising from a concerted process while formation of olefinic product was by an unconcerted path. The formation of *meso* product in the linear case reported here and the partially racemized coupled product account for more ionic or free radical character to the transition state or intermediate than for that of the cyclic cases for both the sodium hydrosulfite reduction reaction and the mercuric oxide oxidation. The apparent larger degree of a concerted mechanism for the cyclic cases may be due to geometric factors.[3]

Since the coupled linear product does exhibit some optical activity, it is improbable that the benzyl residues, whether ionic or radical, have an independent existence in excess of time for racemization.

(3) For a comparison of a linear and a cyclic case of similar structure in an azo decomposition see C. G. Overberger, I. Tashlick, M. Bernstein and R. G. Hiskey, *ibid.*, **80**, 6550 (1958). It was shown that radicals formed from a cyclic compound were more difficult to trap than linear ones of similar structure.

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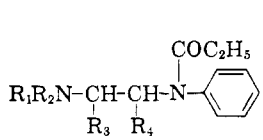
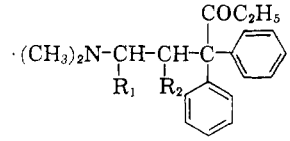
N-(*tert*-AMINOALKYL)-PROPIONANILIDES: A NEW SERIES OF POTENT ANALGESICS

Sir:

We wish to report the establishment of a new series of potent analgesics of novel chemical structure (Ia). The compounds were designed as analogs of methadone (IIa) and isomethadone (IIb) and retain the steric requirements of potent



Ia



II

Ib, $R_1 = C_6H_5(CH_2)_2$, $R_2 = R_3 = CH_3$, $R_4 = H$
Ic, $R_1R_2 = (CH_2)_5$, $R_3 = H$, $R_4 = CH_3$
IIa, $R_1 = CH_3$, $R_2 = H$
IIb, $R_1 = H$, $R_2 = CH_3$

analgesics as set forth by Beckett and Casy and others.[1]

Screening for analgesic activity was accomplished by a sequential modification[2] of the mouse hot plate method of Woolfe and Macdonald.[3] Evaluation of the more active compounds by a modification of the rat tail radiant heat procedure of D'Amour and Smith,[4] and subsequent toxicity studies, led to the selection of N-[2-(methylphenethylamino)-propyl]-propionanilide (Ib) sulfate, *diampromid*, and N-(1-methyl-2-piperidinoethyl)-propionanilide (Ic) hydrochloride, *phenampromid*, as candidates for trial in man. Preliminary clinical results indicate that the potency of diampromid lies between that of meperidine and morphine and the potency of phenampromid approximates that of meperidine.

A benzene solution of methylphenethylamine[5] and 2-bromopropionanilide[6] was heated under re-

(1) (a) A. H. Beckett and A. F. Casy, *J. Pharm. and Pharmacol.*, **6**, 986 (1954); (b) O. J. Braenden, N. B. Eddy and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(2) A. C. Osterberg, J. D. Haynes and C. E. Rauh, *J. Pharm. Acad. Exptl. Therap.*, **122**, 59A (1958). Details of the screening and subsequent pharmacological studies will be reported elsewhere by A. C. Osterberg, *et al.*

(3) G. Woolfe and A. D. Macdonald, *ibid.*, **80**, 300 (1944).

(4) F. E. D'Amour and D. L. Smith, *ibid.*, **72**, 74 (1941).

(5) G. Barger and A. J. Ewins, *J. Chem. Soc.*, 2253 (1910).

(6) A. Tigerstedt, *Ber.*, **25**, 2919 (1892).

flux to give 2-(N-methylphenethylamino)-propionanilide (III), m.p. 65–67°, in 81% yield. The reduction of III with lithium aluminum hydride in tetrahydrofuran afforded 80% of N^2-methyl-N^2-phenethyl-N^1-phenyl-1,2-propanediamine (IV), b.p. 138–144° (0.2 mm.), $n^{27}D$ 1.564. When IV was acylated with propionic anhydride N-[2-(methylphenethylamino)-propyl]-propionanilide (Ib), b.p. 174–178° (0.5 mm.), $n^{26}D$ 1.546, was obtained in 83% yield. The sulfate, m.p. 110–111°, crystallized from ethanol–ether in 85% yield. *Anal.* Calcd. for $C_{21}H_{30}N_2O_5S$: C, 59.7; H, 7.2; N, 6.6; S, 7.6. Found: C, 59.4; H, 7.4; N, 6.6; S, 7.4.

A benzene solution of aniline and 1-(2-bromopropionyl)-piperidine[7] was heated under reflux to give 1-(2-anilinopropionyl)-piperidine (V), m.p. 90–91° in 81% yield. The reduction of V with lithium aluminum hydride in tetrahydrofuran yielded 86% of 1-(2-anilinopropyl)-piperidine (VI), b.p. 108–112° (0.4 mm.), $n^{29}D$ 1.537. Acylation of VI with propionic anhydride gave N-(1-methyl-2-piperidinoethyl)-propionanilide (Ic), b.p. 124–128° (0.2 mm.), $n^{28}D$ 1.518, in 88% yield. The hydrochloride, m.p. 201–202°, was obtained in 88% yield by treating Ic with ethanolic hydrogen chloride and ether. *Anal.* Calcd. for $C_{17}H_{27}ClN_2O$: C, 65.8; H, 8.8; Cl, 11.4; N, 9.0. Found: C, 65.7; H, 8.7; Cl, 11.4; N, 9.3.

(7) C. A. Bischoff, *Ber.*, **31**, 2839 (1898).

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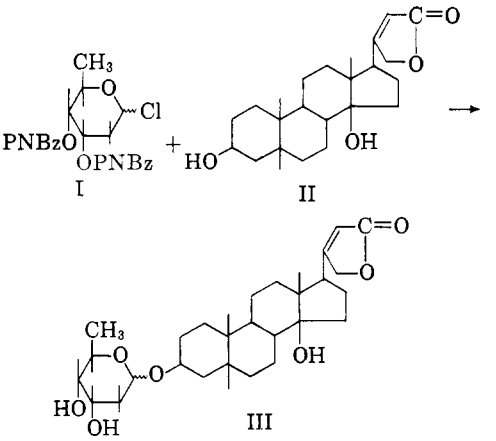
THE PARTIAL SYNTHESIS OF A MONODIGITOXOSIDE OF DIGITOXIGENIN[1]

Sir:

We wish to report the partial synthesis of a monodigitoxoside of digitoxigenin (II) which represents, to our knowledge, the first partial synthesis of a 2′-deoxycardenolide.

By coupling 3,4-di-*O*-*p*-nitrobenzoyl-2,6-dideoxy-D-*ribo*-hexosyl chloride (I)[2] with digitoxigenin (II) in the absence of an acid acceptor, there was obtained an *O*-acylated glycoside which was not isolated; instead, the crude reaction products were saponified *in toto* to give material which, by fractional crystallization, yielded a small quantity of the digitoxoside III, m.p. 253.5–258.5°, $\lambda_{max}^{Me\ alc}$ 218 mμ (characteristic of the α,β-butenolide ring at C_{17}); (*Anal.* Calcd. for $C_{29}H_{44}O_7$: C, 69.00; H, 8.79. Found: C, 68.67; H, 8.74). The compound gave a positive Kedde reaction.

The glycoside III differs from the "natural" monodigitoxoside obtained by Kaiser and coworkers[3]; the infrared spectra of the two compounds, although not identical in all respects, bear



a striking similarity. Paper chromatography in a system designed to separate closely related cardenolides[3] proved III to be homogeneous. It has an R_f value midway between digitoxigenin (II) and Kaiser's monodigitoxoside.[4] Splitting of 0.5 mg. of III in methanol under conditions of transglycosidation and paper chromatography of the resulting material in the same system gave a single spot, coincident in position with digitoxigenin (II). A similar quantity of III (0.4 mg.) was hydrolyzed in a manner to yield the free sugar rather than its methyl glycoside. This was likewise chromatographed, but in a system suitable for sugars only. The result again was a single spot (detected by a reagent employed for deoxy sugars[5]) coinciding exactly with digitoxose (2,6-dideoxy-D-*ribo*-hexopyranose).

The securing of a monodigitoxoside of digitoxigenin different from the "natural" compound is not unexpected, and our III may well be the alternate anomeric form. Since the structure of the "natural" glycoside has not been adduced with certainty, either with respect to the size of the lactol ring of the bound digitoxose or as to anomeric configuration, it is felt that the synthesis reported herein will, ultimately, have an important bearing on these two yet unresolved questions.

Noteworthy also is the fact that our synthesis was accomplished in a classical, yet simple and direct, method, *i.e.*, by converting the 2-deoxy sugar under consideration to an acylglycosyl halide and coupling the latter to the genin II. This obviates the more cumbersome methodology as employed in the synthesis of 2′-deoxyuridine,[6] and of 2′-deoxyadenosine.[7]

Details of this work, which will include configurational assignments, will be published in full at a later date.

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RECEIVED JANUARY 26, 1959

(1) This work was supported by a grant generously awarded by the Washington, D. C., Heart Association.

(2) W. W. Zorbach and T. A. Payne, THIS JOURNAL, **80**, 5564 (1958).

(3) F. Kaiser, E. Haack and H. Spingler, *Ann.*, **603**, 75 (1957).

(4) The authors are greatly indebted to Dr. F. Kaiser for furnishing a small quantity of his monoside which has been of much value in comparison studies.

(5) M. Pöhm and R. Weiser, *Naturwiss.*, **24**, 582 (1956).

(6) D. M. Brown, D. B. Parihar, C. B. Reese and Sir A. Todd, *Proc. Chem. Soc.*, 321 (1957).

(7) C. D. Anderson, L. Goodman and B. R. Baker, THIS JOURNAL, **80**, 6453 (1958).