the microanalyses. Thanks are also due Dr. Frank Short for helpful discussions during the progress of this work.

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6-Phenyl-6-propionoxyperhydrobenzo[c]quinolizines as Potential Analgetics†

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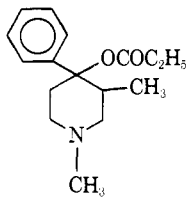
Received November 5, 1973

Much effort has been expended to prepare 4-phenylpiperidine analgetics related to prodine (1). Investigators hoped not only to separate analgetic activity from undesirable side effects but also to shed light on the stereochemical requirements of the analgetic receptor. Some examples are shown in Chart I. Smissman and Steinman[1,2] prepared **2** and **3**; **2** is one-third as active as meperidine while **3** is inactive. In both **2** and **3** the piperidine ring is held in the chair conformation by an adjacent ring. The extra rings also provide bulk which preclude their conforming to the "two carbon fit" at the analgetic receptor. Sam, England, and Temple[3] prepared **4** which is twice as active as meperidine. In **4** boat forms are possible and evidence for one was given.

Chart I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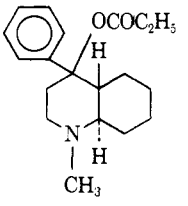
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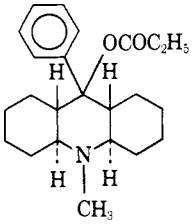
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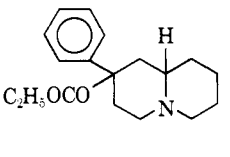
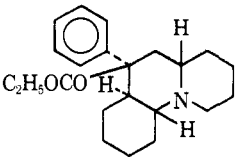
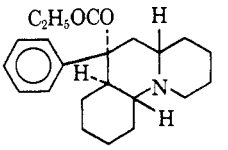

4

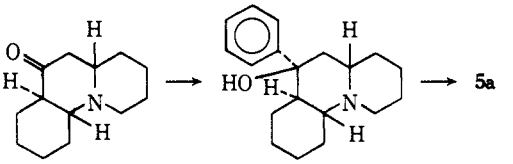
In a continuation of studies involving potential analgetics the related tricyclic compounds **5** were investigated. In **5**, the piperidine ring is held in a chair conformation which, judging from the results with **2** and **3**, would decrease activity. It was of interest, however, to see if the tetramethylene chain between the N and α carbon in **5** would increase the activity as it did in **4**.

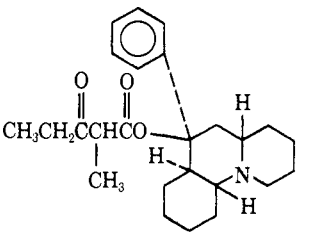

5a


5b

Procedures of Meyers and coworkers[4] and Horii, Morikawa, and Ninomiya[5] were utilized to prepare the starting ketone **6** for the synthesis of **5** as shown in Scheme I.

Scheme I


6 **7** **5a**


8

Treatment of the trans-transoid-trans ketone **6** with phenylmagnesium bromide afforded only the equatorial phenyl isomer **7**. The stereochemistry at C-6 is assumed since only one isomer was obtained (for supportive evidence from analogous systems see ref 1 and 3). The esterification of **7** proved more difficult than anticipated. Attempts using propionic anhydride in pyridine,[2] propionyl chloride in benzene,[6] propionyl chloride and triethylamine in toluene,[7] and propionic acid and *N,N*-carbonyldiimidazole in benzene[8] were unsuccessful. The use of propionyl chloride and triethylamine in toluene gave the β-keto ester **8**. Others have noted that refluxing acyl chlorides in high boiling solvents in the presence of triethylamine produces ketene dimers which react with alcohols to give β-keto esters.[9] Ester **5a** eventually was prepared by the reaction of **7**·HCl with propionyl chloride in acetonitrile.

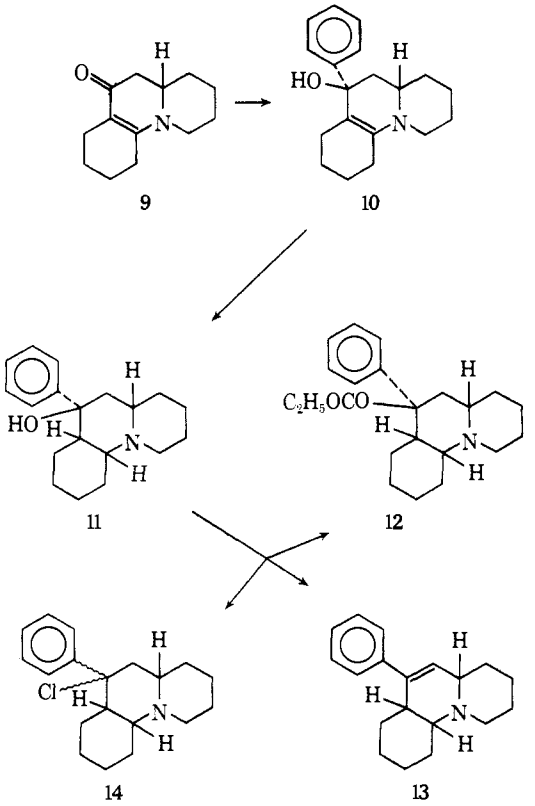
The corresponding cis-transoid-trans-fused isomer **12** was investigated according to the method shown in Scheme II. The reaction of **9** with phenylmagnesium bromide gave a 50% yield of the 1,2-addition product **10**. The hydrogenation of **10** over Pd/C produced one isomer with an R_f (tlc) four times that of **7**; Bohlmann bands in the ir spectra also exist indicating the formation of the cis-transoid-trans-fused isomer **11**. The cis-cisoid-trans-fused isomer would have isomerized to the more stable cis-cisoid-cis-fused isomer.[10] The esterification of **11** according to the method utilized for the preparation of **5a** gave **13** and **14** in a 2:1 ratio and a trace of **12**.

Compounds **5a** and **8** were examined for analgetic activity *via* the hot-plate method[11,12] at sc doses up to 100 mg/kg and were found to be essentially inactive.

† This investigation was supported in part by NIMH Grant No. MH 16973.

‡ Abstracted in part from a dissertation submitted by M. E. Rogers to the Graduate School, University of Mississippi, in partial fulfillment of Doctor of Philosophy degree requirements.

Scheme II



Experimental Section§

Ethyl 2-piperidylacetate was obtained by catalytic hydrogenation of ethyl 2-pyridylacetate (Aldrich). Obtained through literature procedures were *trans-transoid-trans*-perhydrobenzo[c]quinolizin-6-one (6)[6] and 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[c]quinolizin-6-one (9).[4]

trans-transoid-trans-**6(a)-Hydroxy-6(e)-phenylperhydrobenzo[c]quinolizine (7).** The reaction of phenylmagnesium bromide with 20.6 g (0.1 mol) of 6, according to the procedure of Sam and Temple,[13] gave 25.8 g of a semisolid (glc and tlc showed the presence of a small amount of ketone and only one phenyl alcohol) which was recrystallized from a mixture of petroleum ether, Et_2O, and Me_2CO to yield 12.0 g (42%) of solid, mp 156–159°. *Anal.* ($C_{19}H_{27}NO$) C, H, N. The hydrochloride was prepared in the usual way and recrystallized from MeCN, mp 232–234°.

trans-transoid-trans-**6(e)-Phenyl-6(a)-propionoxyperhydrobenzo[c]quinolizine (5a).** A stirred mixture of 8.3 g (0.026 mol) of 7 hydrochloride and 400 ml of MeCN was heated to 60–70° and then treated with a solution of 23.8 g (0.258 mol) of propionyl chloride in 100 ml of MeCN. The mixture was maintained at 60–70° for 120 hr and then concentrated. The residue was treated with 200 ml of cold saturated K_2CO_3. The aqueous mixture was extracted with three 100-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give 9.8 g of a crude mixture which was dissolved in a few milliliters of $CHCl_3$ and absorbed onto 15 g of silica gel and dried. The mixture was added to a 1000 × 25 mm column packed with 150 g of silica gel and eluted with EtOAc at a flow rate of 0.5 ml/min; 15-ml fractions were collected. A combination of fractions yielded 3.1 g of material which was recrystallized from Me_2CO–H_2O to give 2.3 g (25%) of **5a**, mp 125–126°. *Anal.* ($C_{22}H_{31}NO_2$) C, H, N.

trans-transoid-trans-**6(a)-(2-Methyl-3-oxopentanoxy)-6(e)-phenylperhydrobenzo[c]quinolizine (8).** The method of Aboul-Enein and Sam[7] was used. A solution of 2.6 g (0.009 mol) of 7 and 15 ml of triethylamine in 30 ml of anhydrous toluene was treated dropwise for 30 min with a solution of 4.0 g (0.045 mol) of propionyl chloride in 20 ml of dry toluene and then refluxed for 24 hr. The reaction mixture was cooled and the triethylamine hydrochloride removed by filtration. The toluene solution was evaporated, and the residue was treated with 100 ml of 5% $NaHCO_3$. The mixture was extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give 4.0 g of a dark, viscous oil. Trituration of the oil with petroleum ether gave 2.7 g of dark crystals, mp 115–120°, which was dissolved in a few milliliters of petroleum ether and eluted onto a 500 × 25 mm column packed with 100 g of grade I neutral alumina. A flow rate of 6 ml/min was used. A combination of fractions yielded 1.4 g of a dark semisolid which was recrystallized twice from Me_2CO and once from petroleum ether–Et_2O to give 0.6 g (20%) of white crystals, mp 143–144°. *Anal.* ($C_{25}H_{35}NO_3$) C, H, N.

6(a)-Hydroxy-6(e)-phenyl-1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[c]quinolizine (10). The reaction of phenylmagnesium bromide with 4.5 g (0.022 mol) of 9 conducted in Et_2O according to the procedure of Sam and Temple[13] gave 8.5 g of a mixture (tlc showed three spots) which was triturated with petroleum ether to give 3.0 g (50%) of solid: mp 148–149° dec; tlc showed one spot. *Anal.* ($C_{17}H_{25}NO$) C, H, N.

cis-transoid-trans-**6(a)-Hydroxy-6(e)-phenylperhydrobenzo[c]quinolizine (11).** 10 (2 g, 0.007 mol), 100 ml of absolute EtOH, and 0.5 g of 10% Pd/C were hydrogenated at room temperature and 46 psi for 24 hr. The catalyst was removed by filtration and the EtOH evaporated to give 2.2 g of crude oil (tlc showed one spot). The hydrochloride was made in the usual way and recrystallized from MeCN to give 1.9 g of a solid, mp 244–246°. *Anal.* ($C_{19}H_{28}NOCl$) C, H, N.

The hydrochloride (1 g) was converted to the free base which was recrystallized from petroleum ether to give 0.5 g of product, mp 106–108°. *Anal.* ($C_{19}H_{27}NO$) C, H, N.

cis-transoid-trans-6-**Phenyl-1,2,3,4,4a,6a,7,8,9,10,10a-dodecahydro-1*H*-benzo[c]quinolizine (13) and *cis-transoid-trans*-6-Chloro-6-phenylperhydrobenzo[c]quinolizine (14) from the Attempted Esterification of 11.** A mixture of 7.1 g (0.022 mol) of the hydrochloride of 11, 250 ml of MeCN, and 50 ml of propionyl chloride was heated at 60–70° for 12 hr. The reaction mixture was concentrated, and the residue was treated with 100 ml of cold saturated K_2CO_3. The aqueous mixture was extracted with three 100-ml portions of Et_2O. The Et_2O extract was dried over $MgSO_4$ and evaporated to give 9.1 g of an oil. The latter was triturated with petroleum ether to give 1.6 g of crystals which was recrystallized from petroleum ether to yield 0.8 g of 14, mp 130–132° *Anal.* ($C_{19}H_{26}NCl$) C, H, N.

The filtrate from the petroleum ether trituration was eluted onto a 500 × 25 mm column packed with 100 g of grade I neutral alumina. A flow rate of 10 ml/min was used and 50-ml fractions were collected. A combination of fractions yielded 3.4 g of a yellow solid which was recyrstallized twice from MeOH to give 1.6 g of 13, mp 66–67°. *Anal.* ($C_{19}H_{25}N$) C, H, N.

A second combination of fractions from the column gave 0.4 g of a mixture consisting mainly of ester 12.

§ Melting points were determined on a Mel-Temp and are corrected. Ir spectra were taken on either a Perkin-Elmer Model 137 or Perkin-Elmer Model 257 spectrophotometer. Uv spectra were determined in 95% ethanol using a Perkin-Elmer Model 202 spectrophotometer. The nmr spectra were taken on either a Varian Model A-60A or Jeolco Model C-60-HL spectrometer (Me_4Si). Mass spectra were determined on a Du Pont CEC Model 21-492 spectrometer at 70 eV. Spectral data were consistent with assigned structures. Tlc was performed using silica gel thin-layer sheets (Brinkman, Polygram Sil G) or basic alumina thin-layer sheets (Eastman) and varying mixtures of petroleum ether and Et_2O as developers. Glc analyses were performed on a Perkin-Elmer Model 900 chromatograph fitted with flame ionization detectors and two 10 ft by 0.25 in. columns packed with Chromosorb W (60–80 mesh) coated to a concentration of 10% SE-30. Column temperatures of 180–220° were used. A nitrogen carrier flow rate of approximately 30–40 ml/min was used; quantitative measurements were made using the ratio of areas under the peaks method and are not corrected for detector response. Column chromatography was performed using neutral alumina (Woelm) or silica gel (Woelm, 0.05–0.20 mm); the chromatograms were monitored by tlc or glc; like fractions were combined and concentrated. All solvents were evaporated and all reaction mixtures concentrated at water aspirator pressure on a spin evaporator. Elemental analyses were performed by the A. H. Robins Co., Richmond, Va.; values for C, H, and N were obtained and were within ±0.4% of calculated values.

Acknowledgment. Thanks are extended to Dr. Everett May at the National Institutes of Health for the biological data.

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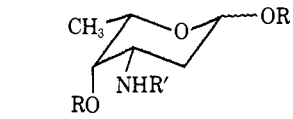
Communications to the Editor

Total Synthesis of the Antitumor Antibiotic Daunorubicin. Coupling of the Sugar and Aglycone

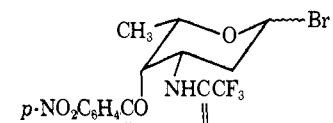
Sir:

The antibiotics daunorubicin†[1,2] (**7**) and especially adriamycin[3] (**7**, with $COCH_3$=$COCH_2OH$) show promise in the clinical treatment of a broad spectrum of human cancers. Adriamycin was recently described as the "most promising new agent under investigation" among anticancer drugs.[4] Daunosamine (**1**, common to both antibiotics) was synthesized previously in these laboratories,[5] and a synthesis of daunomycinone (**5**, the aglycone of **7**) was recently reported.[6] Conversion of daunorubicin (**7**) to adriamycin has been described,[7] so that total synthesis of **7** also constitutes a formal synthesis of adriamycin.

Total synthesis of daunorubicin has now been completed by coupling the suitably protected sugar and aglycone and deblocking the product. Unexpectedly, the coupling was completely stereospecific in that only the natural α-L anomer was formed. *N*-Trifluoroacetyldaunosamine (**2**), mp 146.5–147.0° from ethyl acetate, was obtained from daunosamine hydrochloride. The 1,4-bis(*O*-*p*-nitrobenzoate) **3**, mp 197.0–198.5° from ether–acetone, was suspended in CH_2Cl_2 at 0° and saturated with anhydrous HBr to form a clear solution, from which *p*-nitrobenzoic acid precipitated. Filtration and evaporation afforded the residual 1-bromo sugar **4**. Daunomycinone (**5**), with mercuric cyanide, mercuric bromide, and powdered molecular sieve 3A in anhydrous THF at reflux, was treated with **4** in three portions, each freshly generated from 1 molar equiv of **3** after 0, 22, and 31 hr. After 47 hr the product was detected by tlc on silica gel in ethyl acetate–benzene–methanol (50:50:1) as a red spot under uv or visible light, R_f 0.85, contaminated with **5** (R_f 0.55) and sugar impurities mainly at R_f 0.75 and 0.92. Column chromatography on silica gel separated 22% of unreacted **5**. A second column separated sugar impurities and afforded **6**, estimated to be 80% pure by extinction coefficients in visible and uv spectra. Recrystallization from 95% ethanol gave pure **6** in two crops (50% yield): uv λ_{max} (95% EtOH) 234 nm ($\epsilon \times 10^{-3}$, 43.7), 253 (39.4), 481 (12.5), 496 (12.7), 532 (7.12); fmr ($CDCl_3$, ppm upfield from internal $CFCl_3$) 76.60 (singlet); cmr ($CDCl_3$, ppm from TMS) δ 211.8 (s, MeC=O), 100.3 (d, C-1′), 17.0 (q, C-6′). The pmr spectrum was nearly identical with that[8] for *N*-acetyldaunorubicin, except for downfield shifts of C-4′-H expected from the *p*-nitrobenzoyl groups. The mother liquor residue was purified by preparative tlc on silica gel in ethyl acetate–benzene (1:2) and then by high-pressure liquid chromatography to yield an additional 3%, identical with previous crops in tlc, ir, cmr, pmr, and fmr. Thus, all of the coupling product was isolated and characterized as homogeneous **6** (53% yield), and there was no evidence for any of the β anomer of **6**.



1, R = R′ = H
2, R = H; R′ = CF_3CONH
3, R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO



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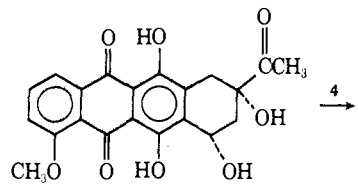
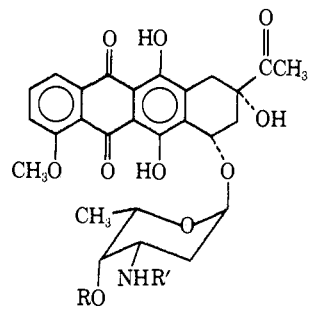


5



6, R = *p*-$NO_2C_6H_3CO$; R′ = CF_3CO
7, R = R′ = H

Deblocking was accomplished by treating a THF solution of **6** (1 g/120 ml) with an equal volume of 0.1 *N* NaOH at 0° for 4.5 hr. The pH was adjusted to 6, THF was evaporated, and after readjustment to pH 9–10, the product was extracted with $CHCl_3$ to yield (94%) daunorubicin free base[9] (**7**), homogeneous on silica gel in acetone–methanol (1:1), R_f 0.55, 90–98% pure by uv and visible extinctions. A $CHCl_3$ solution treated with an equivalent of HCl in ethanol afforded **7**·HCl, precipitated with ether (61% yield): mp 176–181° dec; R_f 0.5 in acetone–methanol (1:1) on silica gel; uv λ_{max} (95% EtOH) 234 nm ($\epsilon \times 10^{-3}$, 37.5), 252 (25.1), 289 (9.24), 480 (12.0), 496 (12.4), 532 (6.54); cmr (D_2O, dioxane internal standard,

†The name daunorubicin has replaced the synonyms daunomycin and rubidomycin. However, the aglycone has retained the name daunomycinone.