and IId are somewhat more effective than the *N*-methyl counterparts.[10,11]

EXPERIMENTAL

Melting points are uncorrected unless otherwise noted. Microanalyses are by Paula M. Parisius of the Institutes Service Analytical Laboratory, Dr. William C. Alford, director.

5,9-Dimethyl-6,7-benzomorphan (IIa) *picrate.* A solution of 1.7 g. of 2,5,9-trimethyl-6,7-benzomorphan (from 2.2 g. of hydrochloride)[10] in 8 ml. of chloroform was added during 0.7 hr. to a stirred solution of 1.0 g. of cyanogen bromide (Eastman) in 10 ml. of chloroform. The solution was refluxed for 2 hr. and evaporated to dryness *in vacuo.* The residue and 36 ml. of 6% hydrochloric acid were refluxed for 20 hr. Cooling and ammonium hydroxide addition liberated an oil which was dried in ether. Evaporation of the ether left 1.5 g. of base which with 1.5 g. of picric acid and 10 ml. of alcohol (heated to solution), gave on cooling to 25° 1.7 g. (50%) of IIa picrate m.p. 232–233° (dec., corr.).

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.60; H, 5.16.

The *hydrochloride* crystallized from acetone-ether in long needles, m.p. 171.5–173.5° (corr.). It was dried 0.5 hr. at 139° for analysis.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 70.71; H, 8.48. Found: C, 70.39; H, 8.35.

2'-Hydroxy-5,9-dimethyl-6,7-benzomorphan (IIb). Two g. of 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan[10] and 4 ml. of acetic anhydride were kept at 95–100° for 0.5 hr., cooled, diluted with ice water, and after 5 min. made alkaline with aqueous potassium hydroxide while keeping ice cold. The oil was quickly shaken into ether. Drying and evaporation of the ether left 2.3 g. of ester which was subjected to *N*-demethylation (1 g. of cyanogen bromide) as described above, except that chloroform or 2:1 benzene butanol was used to extract the crude IIb which weighed 1.8 g. It crystallized from 5 ml. of acetone in a yield of 1.1 g. (60%); m.p. 225–231°, and 232–235° (corr.) after two recrystallizations from methanol.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.20; H, 8.86.

The *hydrochloride,* small prisms from absolute ethanol-ether, melted at 291–294° (dec., corr.).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.25; H, 7.94. Found: C, 66.14; H, 8.13.

N-(3-Oxo-3-phenylpropyl)normorphine (Ic). Normorphine[12] (Ia, 10 g.), 12 g. (1.1 equivalent) of β-dimethylaminopropiophenone methiodide, 3.6 g. (2 equivalents) of sodium carbonate, and 50 ml. of dimethylformamide were agitated with a slow stream of nitrogen which also removed trimethylamine. After 4 hr. addition of water gave an oil which readily crystallized. Filtration and washing with water, then alcohol gave 11.2 g. of Ic which melted at 179–182°. Recrystallization from alcohol yielded 10.0 g. (74%), m.p. 180–183°.

Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25. Found: C, 74.13; H, 6.20.

The Ic, alcoholic sodium hydroxide, and excess methyl iodide were left overnight. The recovered crude product was put in acetone suspension with methyl iodide. The resultant methiodide gave no depression in melting point on admixture with codeine methiodide.

N-(3-Oxo-3-phenylpropyl)norcodeine (Id) *hydrochloride.* This compound was prepared from norcodeine (Ib)[12] as described above. The hydrochloride of Id crystallized from water as the dihydrate, m.p. 168–171°.

Anal. Calcd. for $C_{26}H_{28}ClNO_4.2H_2O$: H_2O, 7.3. Wt. loss (100°), 7.2. For the anhydrous hydrochloride: C, 68.79; H, 6.22. Found: C, 68.80; H, 6.13.

2-(3-Oxo-3-phenylpropyl)-5,9-dimethyl-6,7-benzomorphan (IIc) *hydrochloride.* As described in the synthesis of Ic, the yield of IIc from IIa was 70%. The hydrochloride salt was purified from alcohol; m.p. 181–183°.

Anal. Calcd. for $C_{23}H_{28}ClNO$: C, 74.67; H, 7.63. Found: C, 74.35; H, 7.78.

2'-Hydroxy-5,9-dimethyl-2-(3-oxo-3-phenylpropyl)-6,7-benzomorphan (IId). This compound prepared in 85% yield as described above was freed of a little iodide with dilute aqueous sodium hydroxide. Recrystallized from alcohol, it melted at 175–176°.

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79. Found: C, 78.71; H, 7.89.

2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan (IIf) *methiodide.* Alcoholic sodium hydroxide, IIe[10] and methyl iodide gave after 1 hr. at 25° crystals which were collected and purified from alcohol; m.p. 173–178°.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.71; H, 6.77. Found: C, 52.78; H, 6.98.

Similar treatment of IId gave the same compound, m.p. 170–177°, after purification from alcohol. The melting point was not lowered on admixture with the above sample and the infrared spectra were identical.

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[10] E. L. May and E. M. Fry, *J. Org. Chem.,* **22,** 1366 (1957).

[11] Personal communication from Dr. N. B. Eddy, Chief, Section on Analgesics.

[12] Supplied by Merck & Co. Inc., Rahway, N. J.

Indoxyl Acetate from Indole

ROBERT D. ARNOLD, WILLIAM M. NUTTER, AND WILLIAM L. STEPP

Received July 29, 1958

The observation of Barrnett and Seligman,[1] later extended by others,[2–4] that indoxyl acetate was suitable for the detection of acetylcholinesterase in tissue slices suggested to us that this technique could be adapted to the determination of this enzyme in serum. In the course of our investigations for a method of synthesizing substituted indoxyl acetates that would lend themselves to a colorimetric procedure for the determination of the activity of the enzyme, a new method of preparation of indoxyl acetate was found. Oxidation of indole with various reagents has been reported to give indoxyl[5] but the yields are not good. Halogenated indoles are reported to be inert to alkaline hydrolysis.[6] The usual greater reactivity of iodine compounds compared to that of other halogen compounds, cou-

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[1] R. J. Barrnett and A. M. Seligman, *Science,* **114,** 579 (1951).

[2] R. J. Barrnett, *Ant. Record,* **114,** 577 (1952).

[3] S. J. Holt and R. F. J. Withers, *Nature,* **170,** 1012 (1952).

[4] S. J. Holt and R. F. J. Withers, *J. Physiol.* (*London*), 119, 36P (1953).

[5] O. Baudische and A. B. Hoschek, *Ber.,* **49,** 2580 (1916).

[6] O. Mingoia, *Gazz. chim. ital.,* **60,** 509 (1930).

pled with the observation of Weissgerber[7] that iodine was removed by dilute hydrochloric acid with the production of oxindole, led us to attempt the reaction of 3-iodoindole with silver acetate under mild acidic conditions. We find that in acetic acid solution at room temperature over extended periods of time indoxyl acetate is produced in fair yields. This novel preparation of this class of compounds is expected to open the way to derivatives unobtainable by other routes.

EXPERIMENTAL

3-Iodoindole. A solution of 11.7 g. of indole (0.1 mole) and 4.0 g. (0.1 mole) of sodium hydroxide in 400 ml. of methanol was treated with 101 ml. of iodine–potassium iodide solution containing 25.4 g. (0.2 mole) of iodine with vigorous stirring. No heat was evolved and it was found that the iodine solution could be added as rapidly as possible. Water was added with stirring and the precipitate was filtered and washed with water. This material is unstable and should be used immediately without purification.

Indoxyl acetate. The crude iodoindole was dissolved in 400 ml. of glacial acetic acid and 33.4 g. (0.2 mole) of silver acetate was added in one portion and the suspension was stirred for 20 hr. At the end of this period the mixture was filtered and the filtrate was evaporated to dryness under vacuum. The dark purple residue was recrystallized twice from a 40% solution of methanol in water. The product crystallized as fine white needles which melted at 126° (reported 126–127°).[1] A mixed melting point with an authentic sample of indoxyl acetate was not depressed. The overall yield was 5.4 g. or 28%.

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[7] R. Weissgerber, *Ber.*, **46**, 655 (1913).

Reaction of Carbon Suboxide with Nitro Alcohols

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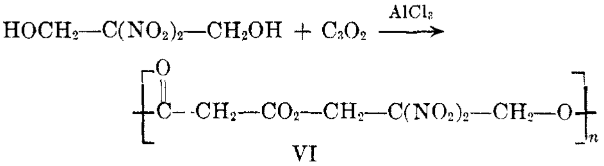
In view of the reactions of carbon suboxide (I) with alcohols,[2] amines, acids and related classes of compounds,[3] it was anticipated that I would also react with primary and secondary nitroparaffins to yield α,α'-dinitro diketones. Since α-nitro ketones possessing alpha hydrogen are unstable compounds, secondary nitro- and *gem*-dinitro compounds were chosen, so that the resulting products would not contain an alpha hydrogen. When 2-nitropropane or 1,1-dinitroethane was treated at room temperature with an ethereal solution of I in the absence of a catalyst or in the presence of such catalysts as sulfuric acid and triethylamine, no addition took place, and the nitro compounds were recovered unchanged. The sulfuric acid caused polymerization of I[2] and the triethylamine formed an addition compound with I which is probably similar to those resulting from the reaction of alkaloids and I.[4]

Since I did not react with nitroparaffins, reactions were initiated with primary, secondary, and tertiary 2-nitroalcohols in order to establish whether the presence of a nitro group adjacent to the reaction center would affect the esterification. It was found that the expected malonic esters formed readily at room temperature, but in small yields unless a catalyst was present. Thus the reaction of 2-nitro-2-methyl-1-propanol (II) with excess of I in ether at room temperature for 24 hours gave di(2-methyl-2-nitropropyl)malonate (III) in only a 39% yield. The yield of III increased to 53% in the presence of sulfuric acid, which, however, also caused extensive polymerization of I. This polymerization was minimized when the reaction was carried out in the presence of hydrogen chloride or aluminum chloride, affording III in yields of 87% and 100%, respectively.

The structure of ester III was established by elemental analysis, and by a mixed melting point determination with an authentic sample of III which was prepared from malonic acid and II and which in its turn analyzed correctly.

Besides compound II, 3-methyl-3-nitro-2-butanol, 2-nitro-1-butanol and 2-nitroethanol (IV) reacted smoothly with I. The ester (V) which was obtained with IV was an oil which could not be distilled even in high vacuum without causing decomposition. However, the structure of V was confirmed by the identity of its infrared spectrum with that of the ester, prepared from IV and malonic acid.

The reaction of I with 2,2-dinitropropanediol yielded a polymeric material.



$$\mathrm{HOCH_2{-}C(NO_2)_2{-}CH_2OH + C_3O_2 \xrightarrow{AlCl_3} \left[\overset{O}{\overset{\|}{C}}{-}CH_2{-}CO_2{-}CH_2{-}C(NO_2)_2{-}CH_2{-}O \right]_n}$$

VI

It was soluble in hot methanol, and on addition of water was partially converted to a solid, the elemental analysis of which was in agreement with the unit structure of polyester VI. The remainder was an oil which could not be solidified.

EXPERIMENTAL

The carbon suboxide was produced by thermal degradation of diacetyltartaric anhydride. Essentially the method of Hurd and Pilgrim[5] was followed, with one variation. The

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[1] From the M.S. dissertation of Robert Miller, Purdue University, May, 1956.

[2] G. Hagelloch and E. Feess, *Ber.*, **84**, 730 (1951).

[3] L. H. Reyerson and Kenneth Kobe, *Chem. Revs.*, **7**, 479 (1930).

[4] O. Diels and K. Hansen, *Ber.*, **59**, 2555 (1926).

[5] C. D. Hurd and F. D. Pilgrim, *J. Am. Chem. Soc.*, **55**, 757 (1933).