TABLE II
PHYSICAL PROPERTIES OF THE 4-SUBSTITUTED 1,2-DIPHENYLETHANOLS

Compd	Mp, °C	Lit. mp, °C	Ref	Calcd, % C	Calcd, % H	Found, % C	Found, % H
V	59–60	59–60	*a*				
VI	57–58	57–58	*b*				
VII	67–68	67–68	*c*				
VIII	67–68	67–68	*d*				
IX	156–157			87.56	7.35	87.42	7.44
X	43–44			77.76	6.06	77.88	6.18
XI	53–54	52–53	*c*				
XII	51–52	51–52	*e*				
XIII	109–110	109–110	*e*				

[a] F. Sachs and L. Sachs, *Ber.*, **38**, 515 (1905). [b] A. Orekhoff and M. Tiffeneau, *Bull. Soc. Chim. Fr.*, **37**, 1410 (1925). [c] A. Feldstein and C. van der Werf, *J. Amer. Chem. Soc.*, **76**, 1621 (1954). [d] Reference 4. [e] Reference 9.

stituent, as measured by σ, increased. This was what would have been expected for an intramolecular hydrogen bond of type III. If the bonding was of type IV, one would have expected either no change in Δ with σ or that the order of Δ with σ would have been opposite to what was found.[8]

In summary, the data tend to indicate that in dilute solution, a form of intramolecular hydrogen bonding resembling III exists for several derivatives of the 1,2-diphenylethanol system. Why this particular type of hydrogen bonding occurs can only be speculated on. However, the answer may lie in the fact that all the substituents studied, with the exception of the nitro group, possess the ability to donate electron density to the ring either by induction or resonance. This donation of electron density may be the driving force which enables the OH to bond with the phenyl ring possessing the substituent. It is noteworthy that the NO_2-substituted alcohol is the only one which fails to give a second band in the near ir. More information is currently needed before a complete picture can be developed. Further work is continuing in our laboratories.

Experimental Section

Instrumentation.—Near-infrared spectra were recorded on a Cary 14 recording spectrophotometer. Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected.

Preparation of Compounds.—Compounds V–XII were prepared using the procedure illustrated by the preparation of 4-fluoro-1,2-diphenylethanol below. Compound XIII was prepared according to the procedure of Noyce.[9] All the physical data for compounds V–XIII is summed up in Table II.

Preparation of 4-Fluoro-1,2-diphenylethanol.—In a 500-ml, round-bottom flask equipped with a reflux condenser and a mechanical stirrer, a solution of benzylmagnesium chloride was made by adding benzyl chloride (13 g, 0.11 mol) to magnesium (2.4 g, 0.1 g-atom) in 100 ml of ether. A solution of 4-fluorobenzaldehyde (12.4 g, 0.1 mol) in 50 ml of ether was added over a 10-min period with stirring. After stirring for 2 hr the solution was hydrolyzed using a saturated ammonium chloride solution. The ether layer was filtered off. After the ether was removed under reduced pressure, the remaining solid was taken up in heptane and crystallized, mp 43–44°. The yield was 0.064 mol (64%).

Registry No.—V, 31233-60-0; VI, 5422-47-9; VII, 20498-63-9; VIII, 614-29-9; IX, 31233-64-4; X, 23096-47-1; XI, 31233-66-6; XII, 20498-64-0; XIII, 20498-66-2.

(8) Electron-withdrawing substituents on benzyl alcohols have been shown to strengthen the proton donor ability of the OH, resulting in a lower frequency of absorption for the OH when it forms a bond with any species besides the phenyl ring. See ref 3b.

(9) D. S. Noyce, D. R. Hartter, and R. M. Pollack, *J. Amer. Chem. Soc.*, **90**, 3794 (1968).

Formylation of Amines with Phenyl Formate

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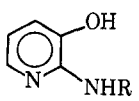
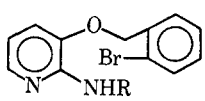
Conventional formylation procedures with 2-amino-3-pyridinol (**1**) or 2-amino-3-(*o*-bromobenzyloxy)pyridine (**2**) gave principally the formic acid salts **3** and **4**, respectively, and attempts, under a variety of conditions, to dehydrate **3** or **4** yielded tars rather than the corresponding *N*-formyl derivatives **5** and **6**. Eventually, **6** was prepared in 50% yield from **2**, HCO_2H, and dicyclohexylcarbodiimide;[1] the same procedure with **1**, however, failed to give **5**.



1, R = H
3, R = H·HCO_2H
5, R = CHO
8, R = CH_3CO



2, R = H
4, R = H·HCO_2H
6, R = CHO

In the search that ensued to uncover other formylation procedures for both **1** and **2**, it was found that phenyl formate (**7**) was a uniquely effective reagent that converted both **1** and **2** to **5** and **6**, respectively, in very high yields. The same reagent was also useful for converting a variety of aliphatic, aromatic, and heterocyclic amines to their *N*-formyl derivatives.[2]

In this procedure, the amine was mixed with a slight excess of **7** that had been cooled to 0°. Reaction was spontaneous, even at 0°, and sufficiently exothermic to raise the temperature of the mixture to 20–30°. In some instances the product crystallized from the reaction mixture and could be isolated by filtration. When the product was soluble, the mixture of phenol and any unreacted **7** was distilled *in vacuo* and the product isolated from the residue. The yields ranged from 60 to 95%.

(1) H. L. Yale and J. Pluscec, *J. Org. Chem.*, **35**, 4254 (1970).

(2) There are no reports in the literature of the use of phenyl formate as a formylating agent.

TABLE I
REACTIONS OF PHENYL FORMATE

Reactant	Product[a]	Registry no.	Yield, %[b]	Mp or bp, °C
o-Bromoaniline	*o*-Bromoformanilide		90	87–88[c]
m-Bromoaniline	*m*-Bromoformanilide		95	56–58[d]
p-Chloroaniline	*p*-Chloroformanilide		85	99–101[e]
α,α,α-Trifluoro-*m*-toluidine	α,α,α-Trifluoro-*m*-formotoluidide	657-78-3	87	49–51
o-Aminophenol	*o*-Hydroxyformanilide		95	128–130[f]
2-Amino-4-chlorophenol	5-Chloro-2-hydroxyformanilide	31354-50-4	95	164–165
o-Phenylenediamine	*N,N'*-(*o*-Phenylene)diformamide	31354-51-5	94	155–157 dec
2,2'-Dithiobis(4-chloroaniline)	2,2'-Dithiobis(4-chloroformanilide)	31354-52-6	60	185–187
Benzylamine	*N*-Benzylformamide		83	57–58[g]
o-(*o*-Bromobenzyloxy)aniline	*o*-(*o*-Bromobenzyloxy)formanilide		70	113–114[h]
p-Nitrobenzamidoxime	*N*-Formyl-*p*-nitrobenzamidoxime	31354-53-7	85	138–139 dec
4,4'-Trimethylenedipiperidine	4,4'-Trimethylenebis(1-piperidinecarboxaldehyde)	31354-54-8	95	225 (0.9 mm)
2-Aminopyridine	*N*-(2-Pyridyl)formamide		95	71–73[i]
3-Aminopyridine	*N*-(3-Pyridyl)formamide		72	90–91[i]
4-Aminopyridine	*N*-(4-Pyridyl)formamide	22236-91-5	68	151–153
4,6-Dimethyl-2-aminopyridine	4,6-Dimethyl(2-pyridyl)formamide	31354-56-0	60	98–100
2-Aminopyrimidine	*N*-(2-Pyrimidinyl)formamide	31354-57-1	78	208–210
2-Amino-5-phenyl-1,3,4-oxadiazole	*N*-(5-Phenyl-1,3,4-oxadiazol-2-yl)formamide	31354-58-2	64	150–152
Piperazine	1,4-Piperazinedicarboxaldehyde	4164-39-0	88	122–123

[a] Satisfactory analytical data (±0.35% for C, H, and N) were reported for all new compounds listed in the table. [b] From 1.0 g of amine and 2.0 ml of 35% phenyl formate. [c] F. D. Chattaway and K. J. P. Orton [*Chem. Ber.*, **33**, 2396 (1900)] report mp 87°. [d] O. C. M. Davis and F. W. Rixon [*J. Chem. Soc.*, **107**, 728 (1915)] report mp 62–63°. [e] F. D. Chattaway, K. J. P. Orton, and W. H. Hurtley [*Chem. Ber.*, **32**, 3635 (1899)] report mp 102°. [f] E. Bamberger [*ibid.*, **36**, 2042 (1903)] report mp 129–129.5°. [g] C. A. Buehler and C. A. Mackenzie [*J. Amer. Chem. Soc.*, **59**, 421 (1937)] report mp 59.8–60.4°. [h] H. L. Yale and F. Sowinski [*J. Med. Chem.*, **7**, 609 (1964)] report mp 113–114°. [i] F. F. Blicke and M. U. Tsao [*J. Amer. Chem. Soc.*, **68**, 905 (1946)] report mp 71°. [j] E. Plazek, A. Marcinikow, and C. Stammer [*Rocz. Chem.*, **15**, 365 (1935); *Chem. Abstr.*, **30**, 1377[8] (1936)] report mp 96°.

All attemps to prepare **7** in pure form have been unsuccessful and **7** has always been contaminated with phenol and trace amounts of other impurities.[3] It was significant that these formylations could be effected with crude, undistilled or distilled, **7** that contained from 40 to 60% of phenol and 2 to 5% of unidentified impurities as determined by glc analysis.

While pure phenyl acetate can be prepared, it did not react with **1** at 0 or 20°, even when phenol was added; prolonged heating at 65° gave **8** but in low yield and some **1** was recovered.

Primary and secondary amines reacted with **7**, with the former yielding only NHCHO derivatives. Other phenolic groups, *e.g.*, in *o*-aminophenols or *o*-aminopyridinols, did not react. Diamines, *e.g.*, *o*-phenylenediamine, gave the *o*-(*N,N'*-diformyl) derivatives. 2-Amino-5-phenyl-1,3,4-oxadiazole, that could not be formylated by conventional methods or by HCO_2H and dicyclohexylcarbodiimide, although the acetylated derivative was readily prepared,[4] was formylated by **7**. Interestingly, **7** and the formic acid salt **3** did not react and the **3** was recovered. Finally, amidoximes reacted readily to give the C(:NOH)NHCHO derivatives. Table I summarizes the relevant data for some typical reactions. Acetylation of **5** with Ac_2O at 25° gave *N*-(3-acetoxy-2-pyridyl)formamide (**9**) while alkylation of **5** with *o*-bromobenzyl bromide gave **6**.

Experimental Section

***N*-(3-Hydroxy-2-pyridyl)formamide (5).**—To 490.0 g of crude undistilled **7** [50% **7**, 45% PhOH, 5% unidentified, $n^{27}D$ 1.5040 (2.0 mol)] at 0° was added, with stirring, 205 g (1.87 mol) of **1**. A solution formed as the temperature rose slowly to 30°. Stirring was continued until it was stopped by the mixture becoming solid. To this was added 1500 ml of $(i\text{-Pr})_2O$; the stirring was initiated, the whole mixture was stirred for 1 hr and the solid was filtered and air-dried to give 221.0 g of crude **5**, mp 160–161° dec. Distillation of the filtrate, first to remove $(i\text{-Pr})_2O$, and then **7** and PhOH [bp *ca.* 45° (1 mm)] left a residue of 84.6 g. This was agitated with 100 ml of $(i\text{-Pr})_2O$ to give 42.6 g of additional crude **5**, mp 158–160° dec. Recrystallization of the combined crude products from EtOAc gave 234.9 g (91% yield) of **5**: mp 163–164° dec; ν (KBr) 3210–2800 (s, broad), 1670 cm^{-1} (s).

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.19; H, 4.38; N, 20.28. Found: C, 52.07; H, 4.48; N, 20.44.

***N*-(3-Acetoxy-2-pyridyl)formamide (9).**—When 0.50 g of **5** and 3 ml of Ac_2O were mixed at 25°, solution occurred in 2 hr. The solution was concentrated *in vacuo* at 90° and the residue recrystallized from $(i\text{-Pr})_2O$ to give 0.50 g (78% yield) of **9**: mp 127–129° dec; ν ($CDCl_3$) 3400 (s), 1770 (s), 1690 cm^{-1} (s).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.32; H, 4.48; N, 15.54. Found: C, 53.28; H, 4.67; 15.51.

***N*-[3-(*o*-Bromobenzyloxy)-2-pyridyl]formamide (6). A.**—To a suspension of 351.0 g (2.5 mol) of **5** in 1.4 l. of absolute EtOH was added in 0.5 hr 135 g (2.5 mol) of MeONa in 1650 ml of absolute EtOH, maintaining the temperature at 25°. After the addition was completed (5 min), the mixture solidified. An additional 150 ml of absolute EtOH has added, stirring initiated, and 625 g (2.5 mol) of *o*-bromobenzyl bromide added in 0.5 hr at 25°. When the addition was completed, a small sample diluted with H_2O indicated a pH of 8.5 and the pH was unchanged at 25° after an additional 2 hr of stirring. The mixture was heated; at 65°, the pH was 7.5; at reflux temperature, after a total of 12 min of heating, the pH was 6.9; and after 0.25 hr the pH was 5.8. Heating was terminated, the mixture was allowed to cool spontaneously to 40° and cooled in ice, and the solid was filtered, washed with H_2O, and air-dried to give 660.0 g (86% yield) of crude **6**, mp 132–135°. Recrystallization from EtOAc gave 594.0 g (78% yield) of **6**, mp 137–139°; a mixture melting point with a sample of **6**, prepared as described in the previous paper, was 137–139° and their ir spectra were superimposable.

B.—When **2**, 10.7 g (0.04 mol), and 19.6 g (0.04 mol) of 50% **7** were mixed at 0°, the temperature rose to 25° and a clear solution formed. On keeping at room temperature, a solid separated. This was filtered to give 10.1 g of crude **6**, mp 134–136°. Recrystallization from EtOAc gave 8.7 g (74% yield) of **6**, mp 137–139°, identical in all respects with **6** repared as in A.

Formic Acid Salt of 1 (3).—A solution of 19.8 g (0.18 mol) of

(3) The literature on the synthesis of **7** has been reviewed by W. Stevens and A. Van Es, *Recl. Trav. Chim. Pays-Bas*, **83**, 1294 (1964).

(4) H. L. Yale and K. Losee, *J. Med. Chem.*, **9**, 478 (1966).

1 in 50 ml of 98–100% HCO_2H was heated under reflux for 1 hr and then concentrated at 90° *in vacuo*. The residual solid, 22.3 g, melted at 117–119°. Recrystallization from EtOAc gave 17.8 g (64% yield) of **3**: mp 125–127°; ν (mineral oil) 3340 (s), 3100 (s), 2700–2400 (s, broad), 1665 cm^{-1} (s).

Anal. Calcd for $C_5H_6N_2O \cdot HCO_2H$: C, 46.13; H, 5.17; N, 17.94; neut equiv, ($HClO_4$ in glacial AcOH), 156. Found: C, 46.11; H, 5.11; N, 18.00; neut equiv, 157. (Note: 2-aminopyridines are monobasic toward $HClO_4$ in glacial ACOH, *e.g.*, 2-aminopyridine, mol wt 94, gives neut equiv 93).

When **1** and 98–100% HCO_2H were heated for 24 hr, **3** was the only product; **1** and HCO_2H–Ac_2O gave **3**; **1** and HCO_2COCH_3 gave **3**; **1**, HCO_2H, and $C_6H_{11}N{=}C{=}NC_6H_{11}$ in EtOAc gave only highly colored, high-melting materials that could not be identified; and **1** and HCO_2Me or HCO_2Et heated in sealed tubes for 18 hr at 125–150° gave only **3** as the identifiable product.

Formic Acid Salt of 2 (4).—A solution of 18.0 g (0.16 mol) of **2** and 90 ml of HCO_2COCH_3 was heated at 60° for 21 hr and then concentrated at 70° *in vacuo*. The residual oil crystallized spontaneously; it weighed 21.2 g (83% yield), mp 72–74°. Recrystallization from $(i\text{-Pr})_2O$ gave 17.2 g (69% yield) of **4**: mp 78–80°; ν (KBr) 3370 (s), 2840 (m), 1680 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{11}BrN_2O \cdot HCO_2H$: C, 48.02; H, 4.03; N, 8.62. Found C, 48.21; H, 3.96; N, 8.88.

Alternative procedures, *e.g.*, heating **2** with HCO_2H, with or without Ac_2O, under reflux or heating **2** HCl, HCO_2Na, and HCO_2H under reflux, gave **4**; **2** and Cl_3CCHO in $CHCl_3$ did not react.

Reaction of 1 with PhO_2CCH_3. Preparation of 8.—A mixture of 1.0 g (0.091 mol) of **1** and 2.2 g of PhO_2CCH_3 was kept at 0° and then at 25° for 4 days; only **1** was recovered. No reaction occurred following the addition of 0.5 g of PhOH. When the same reactants were heated for 4 hr at 65° and the mixture was concentrated *in vacuo*, a residue, 1.0 g, mp 93–99°, was obtained. This was dissolved in 10 ml of boiling PhMe, the hot solution filtered, and the filtrate cooled to give 0.15 g of **1**. Concentration of the filtrate to dryness gave 0.60 of crude **8**, mp 102–105°. Recrystallization from $(i\text{-Pr})_2O$ gave 0.30 g (22% yield) of **8**: mp 102–104°; ν ($CDCl_3$) 3400 (s), 3000–2600 (s, broad), 1655 cm^{-1} (s).

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.31; N, 18.41. Found: C, 55.19; H, 5.44; N, 18.61.

Preparation of Phenyl Formate.—To 470.0 g (5.0 mol) of phenol and 1100 g (23.5 mol) of 98–100% HCO_2H was added in 0.5 hr 1120.0 g (7.3 mol) of $POCl_3$, and then, in one portion, 30.0 g (0.225 mol) of $AlCl_3$. The temperature rose spontaneously to 40°. The mixture was stirred without cooling for 2 hr and heated so that the internal temperature rose to 70° in 2 hr, and the temperature was maintained at 70° for 5 hr. The ice-cooled mixture was agitated and then diluted slowly with 1500 ml of ice-cooled H_2O-saturated Et_2O and then with 1500 g of ice. The H_2O layer was separated, 1500 ml of H_2O added, and the cooled mixture treated with solid $NaHCO_3$ until the pH was 7.5. The H_2O layer was again separated, and the Et_2O layer was washed with 500 ml of saturated H_2O–NaCl, dried, and concentrated. The residue weighed 615.3 g, $n^{26}D$ 1.5195, d^{20}_{20} 1.12. Analyses by glc indicated 65% phenyl formate, 33% phenol, and 2% unidentified impurities. The yield was 65%. The undistilled material was suitable for use; it could be distilled, bp 72–74° (13 mm), but the distilled material had the same composition as the crude product.

Registry No.—**3**, 31354-43-5; **4**, 31354-44-6; **5**, 31354-45-7; **6**, 26372-72-5; **7**, 1864-94-4; **8**, 31354-48-0; **9**, 31354-49-1.

A Total Synthesis of the Four Isomeric 2-Tropanols

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As part of an extensive study of pharmacologically active derivatives of L(+)-2α-tropanol and L(−)-2β-tropanol, it was necessary to demonstrate the feasibility of a total synthesis of these alcohols from commercially available raw materials; the quantities that might be required could not be prepared from available supplies of cocaine by the Bell and Archer synthesis.[1] It was also important to prepare the hitherto undescribed D(−)-2α-tropanol and D(+)-2β-tropanol to permit parallel studies of their derivatives.

Two total syntheses of L(+)-2α-tropanol from pyrrole in overall yields of 10–18% have been described;[2] optical resolution was achieved at the 2-tropanone stage. Recently R. E. Lyle and his associates[3] reported that the hydroboration–oxidation of tropidine gave L(+)-2α-tropanol in 43% yield, along with 50% of 3α-tropanol and small amounts of the β isomers. Since tropidine can be prepared from 3α-tropanol, and the latter by the well-known Robinson–Schöpf reaction, Lyle's work completes another total synthesis of the 2-tropanols. The novel total synthesis of anhydroecgonine[4,5] from benzene and diazoacetic ester by way of cycloheptatrienecarboxylic acid constitutes the first portion of still another total synthesis, for anhydroecgonine amide is an intermediate in the Bell and Archer synthesis. A study of the process economics of all these routes showed that they were unsatisfactory for large-scale synthesis.

We have used the synthesis shown in Scheme I to prepare racemic 2α-tropanol (**6**) from commercially available acetonedicarboxylic acid and 2,5-diethoxytetrahydrofuran in 25% overall yield; the starting materials can be made in high yield from citric acid and furan, respectively. The route shown was a simple combination of Findlay's synthesis[6,7] of **3** (now known[8] to be allopseudoecgonine) with the procedures used by Bell and Archer for the conversion of ecgonine to L(+)-**6**. Optical resolution of racemic **6** was achieved in high yield through appropriate salts of (+)-and (−)-tartaric acids. The novel D-(−)-2α-tropanol was epimerized to the novel D(+)-2β-tropanol by a procedure used previously for epimerization of the L(+)-2α isomer.[1]

Experimental Section[9]

2-Methoxycarbonyl-3-tropanone (1).—Findlay's procedure[6] was carried out at two–four times the scale used by him. The

(1) M. R. Bell and S. Archer, *J. Amer. Chem. Soc.*, **82**, 4642 (1960).

(2) W. A. M. Davies, A. R. Pinder, and I. G. Morris, *Tetrahedron*, **18**, 405 (1962).

(3) R. E. Lyle, K. R. Carle, C. R. Ellefson, and C. K. Spicer, *J. Org. Chem.*, **35**, 802 (1970).

(4) C. Grundmann and G. Ottmann, *Justus Liebigs Ann. Chem.* **605**, 24 (1957).

(5) C. J. Grundmann and G. Ottmann (to Olin-Mathieson Chemical Corp.), U. S. Patent 2,783,235 (1957).

(6) S. P. Findlay, *J. Org. Chem.*, **22**, 1385 (1957).

(7) S. P. Findlay, *ibid.*, **24**, 1540 (1959).

(8) A. Sinnema, L. Maat, A. J. Van der Gugten, and H. C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, **87**, 1027 (1968). This article reviews all earlier syntheses and establishes the correct configuration for the four isomeric ecgonines and the cocaines derived therefrom. The assigned configurations differ from those assigned by some earlier workers.

(9) Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Dr. S. M. Nagy (Belmont, Mass.). Satisfactory ir and nmr spectra were recorded for all compounds. Analytical glc procedures for the 2-tropanols involved the use of an F & M 1609 instrument with a flame ionization detector. The 6-ft stainless steel column contained 5% Carbowax 20M on Haloport F and was operated at 150° with helium as a carrier gas at 20 ml/min. Under these conditions the retention times were for 2β-tropanol, 7–8 min; 2-tropanone, 11–12 min; 2α-tropanol, 16–17 min. The relative retention times were similar to those reported for analogous compounds in the 3-tropanol series by H. S. Aaron, G. E. Wicks, and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).